A married couple comes to the physician for routine prenatal counseling. The husband is 120 cm (3 ft 11 in) tall with disproportionately short upper and lower extremities, a large head, and a prominent forehead. He is unable to provide a biological family history as he was adopted. His spouse is of average height with normal constitutional features, and her family history is insignificant. They are concerned about their unborn child's height. Which of the following is the best response to their concerns?

A. The condition is not inheritable

B. The risk depends on the child's biological sex

C. The risk depends on the mother's carrier status

D. The risk for the child to be short is about 25%

E. The risk for the child to be short is about 50%

Submit

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- A. The condition is not inheritable (7%)
- B. The risk depends on the child's biological sex (3%)
- C. The risk depends on the mother's carrier status (13%)
- D. The risk for the child to be short is about 25% (7%)
- ✓ E. The risk for the child to be short is about 50% (68%)

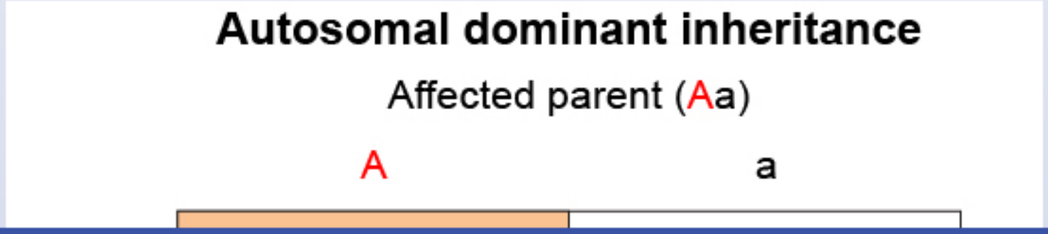
Omitted
Correct answer
E

68%
Answered correctly

01 min, 21 secs
Time Spent

04/12/2020
Last Updated

Explanation



Autosomal dominant inheritance

Affected parent (Aa)

Normal parent (aa)	A	a
a	Aa Affected child	aa Normal child
a	Aa Affected child	aa Normal child

Offspring have 50% chance of being affected

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The husband's short stature and morphologic features are suggestive of **achondroplasia**. Achondroplasia is the most common form of short-limbed dwarfism and is caused by a mutation that results in constitutive activation of **fibroblast growth factor receptor 3 (FGFR3)**.

Achondroplasia occurs as a sporadic mutation (due to advanced paternal age) in 85% of cases. However, once a mutation occurs, it can be transmitted as an **autosomal dominant** trait (responsible for the remaining 15% of cases) **(Choice A)**. Only **1 mutant copy** of the FGFR3 gene is sufficient to cause the disorder; **2 copies** of the mutant gene (ie, homozygosity) are **lethal**. As a result, the husband must be heterozygous for the achondroplasia mutation.

A **heterozygous parent** has a **50% chance** of transmitting an autosomal dominant mutation. Therefore, the unborn child has a 50% chance of inheriting achondroplasia. Because achondroplasia is a rare condition, the chance of the unborn child having a sporadic (de novo) mutation does not significantly add to the 50% risk of inheriting the disease.

(Choice B) In sex-linked disorders, the responsible gene is located on a sex chromosome (either X or Y). Most sex-linked disorders are X-linked recessive (XLR). In XLR disorders, women with a copy of the defective gene will not have the disorder but will be carriers; men who inherit the defective gene will be affected. In X-linked dominant disorders, both males and females are affected following inheritance of the defective gene.

(Choice C) Inheritance of an AD trait does not always result in the disease phenotype in conditions with incomplete penetrance. However, achondroplasia is a fully penetrant genetic disorder; if the mother carried the trait, she would have short stature.

(Choice D) About 25% of children are affected in autosomal recessive (AR) disorders if both parents carry 1 copy of the defective gene (most common scenario). Many AR disorders are the result of enzymatic deficiencies (eg, phenylketonuria) that require both copies of the gene to be knocked out, as 1 functional copy usually provides sufficient activity to prevent occurrence of the disease.

Educational objective:
Achondroplasia is an autosomal dominant (AD) disorder that results in a gain-of-function mutation in the FGFR3 gene. Most individuals affected by AD disorders are heterozygous and have a 50% chance of transmitting the mutation to their offspring.

References

- Achondroplasia
- Achondroplasia: from genotype to phenotype.

Exhibit Display

X-linked recessive inheritance

Affected father

Father \ Mother	X	X	
Xd	XXd	XXd	All daughters are carriers
Y	XY	XY	All sons are normal

Carrier mother

Father \ Mother	X	Xd	
X	XX	XXd	Daughters have 50% chance of becoming carriers
Y	XY	XdY	Sons have 50% chance of being affected

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- Achondroplasia: from genotype to phenotype.

Exhibit Display

X-linked dominant inheritance

Affected father

Father \ Mother	X	X
Xd	XXd	XXd
Y	XY	XY

All daughters are affected

All sons are normal

Affected mother

Father \ Mother	X	Xd
X	XX	XXd
Y	XY	XdY

All sons & daughters have 50% chance of being affected

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- Achondroplasia: from genotype to phenotype.

Exhibit Display

Autosomal recessive inheritance

Carrier parent (Aa)

Carrier parent (Aa)	A	a
A	AA Normal child	Aa Carrier child
a	Aa Carrier child	aa Affected child

Offspring have 25% chance of being affected

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- Achondroplasia: from genotype to phenotype.

A researcher is studying the Fas receptor (FasR), a protein widely expressed on cell surfaces. The signaling cascade of programmed cell death is initiated when FasR binds to its ligand (FasL), which is expressed on cytotoxic T cells. In an experiment, cancer cells that escaped elimination by the immune system were found to contain soluble Fas proteins that did not promote apoptosis. The soluble Fas proteins were shorter and lacked the transmembrane domain. DNA analysis of these cells revealed no *FAS* gene mutations. Which of the following is the most likely explanation for the formation of altered Fas proteins in these cancer cells?

- A. Alternative splicing
- B. Defective polyadenylation
- C. DNA methylation
- D. Polycistronic mRNA
- E. Protein ubiquitination

Submit

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- ✓ A. Alternative splicing (70%)
- B. Defective polyadenylation (7%)
- C. DNA methylation (11%)
- D. Polycistronic mRNA (3%)
- E. Protein ubiquitination (8%)

Omitted
Correct answer
A

70%
Answered correctly

02 secs
Time Spent

03/04/2020
Last Updated

Explanation

Transcription

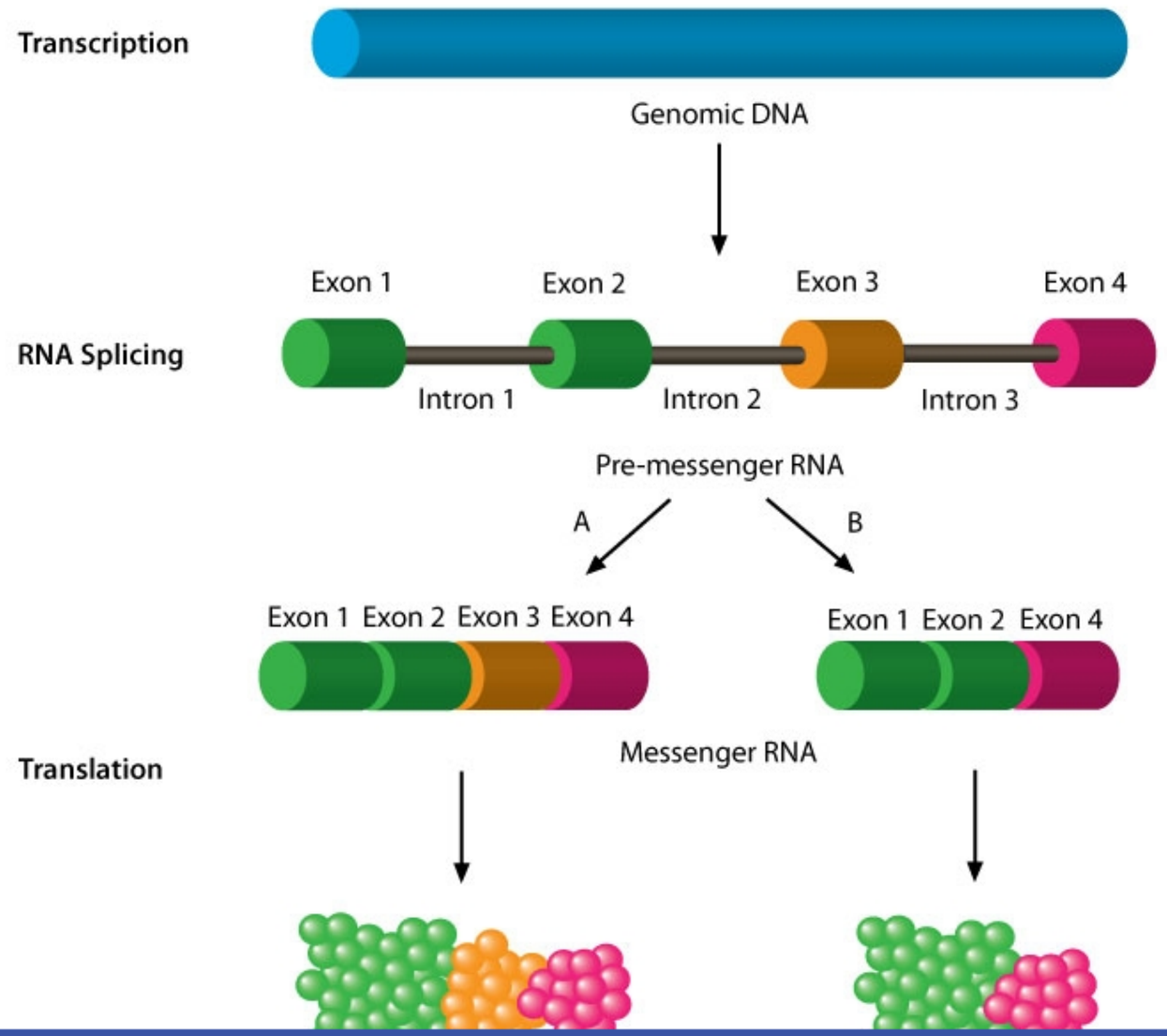
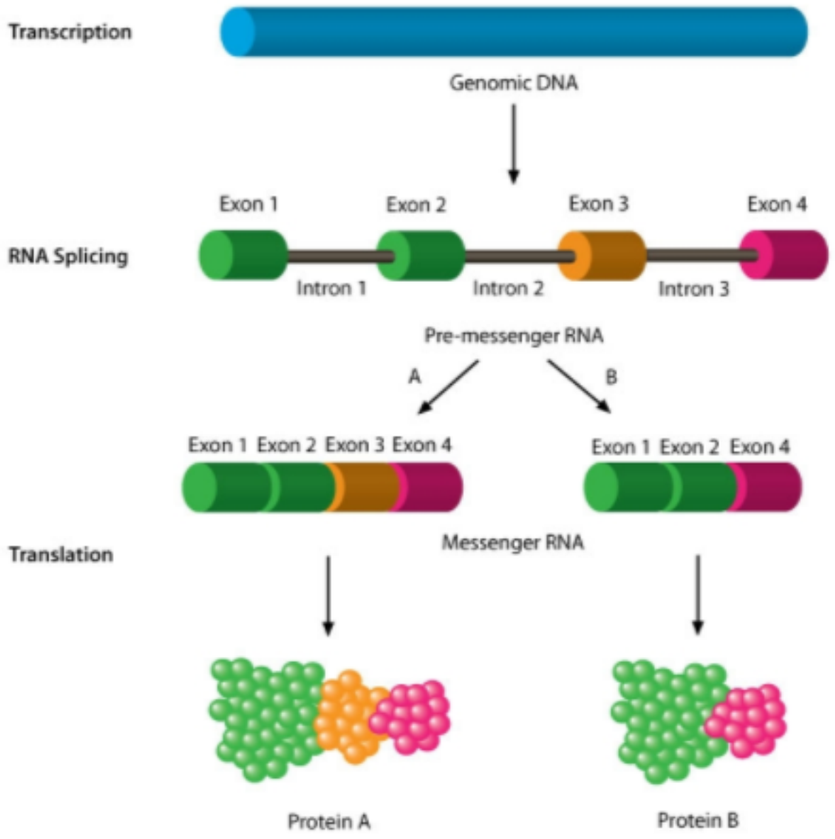

Transcription
Genomic DNA
RNA Splicing
Exon 1
Exon 2
Exon 3
Exon 4
Intron 1
Intron 2
Intron 3
Pre-messenger RNA
A
B
Exon 1 Exon 2 Exon 3 Exon 4
Exon 1 Exon 2 Exon 4
Translation
Messenger RNA

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Alternative splicing is a process by which different combinations of DNA coding regions **(exons)** are selectively included or excluded from a mature messenger RNA (mRNA) transcript. This allows the DNA contained in a single gene to code for a functionally diverse group of proteins.

Splicing is a post-transcriptional modification that removes noncoding DNA regions **(introns)** from precursor-mRNA (pre-mRNA). The process is driven by a large protein complex **(spliceosome)** comprised of small nuclear ribonucleoproteins (snRNPs). Pre-mRNA splice sites are bound by the spliceosome, forming a lariat-shaped intermediate containing the introns. This intermediate is excised and the exons are joined, completing the splicing process.

Alternative splicing is a normal process that allows production of alternate sets of proteins in different tissues. It has also been implicated in various human diseases. Cancers in particular can use alternative splicing to evade innate defense mechanisms. The Fas receptor-Fas ligand interaction drives programmed cell death via the cytotoxic T-cell mediated extrinsic pathway. Cancer cells may develop the ability to **splice out** a particular exon that codes for the **transmembrane domain** of the Fas receptor (FasR), converting it to a soluble form that is not expressed on the cell surface, which allows the cells to **evade apoptosis**.

(Choice B) Polyadenylation is a post-transcriptional modification in which a tail comprised of multiple adenosine nucleotides is added to the 3' end of a new mRNA transcript. This process is necessary for the nuclear export and cytoplasmic stability of mRNA.

(Choice C) DNA methylation describes the process by which methyl groups are added to DNA, suppressing transcription of the methylated genes.

(Choice D) Polycistronic mRNA is often found in bacteria and contains multiple open reading frames that are translated into several proteins. In contrast, eukaryotic organisms have monocistronic mRNA, which codes for only one protein.

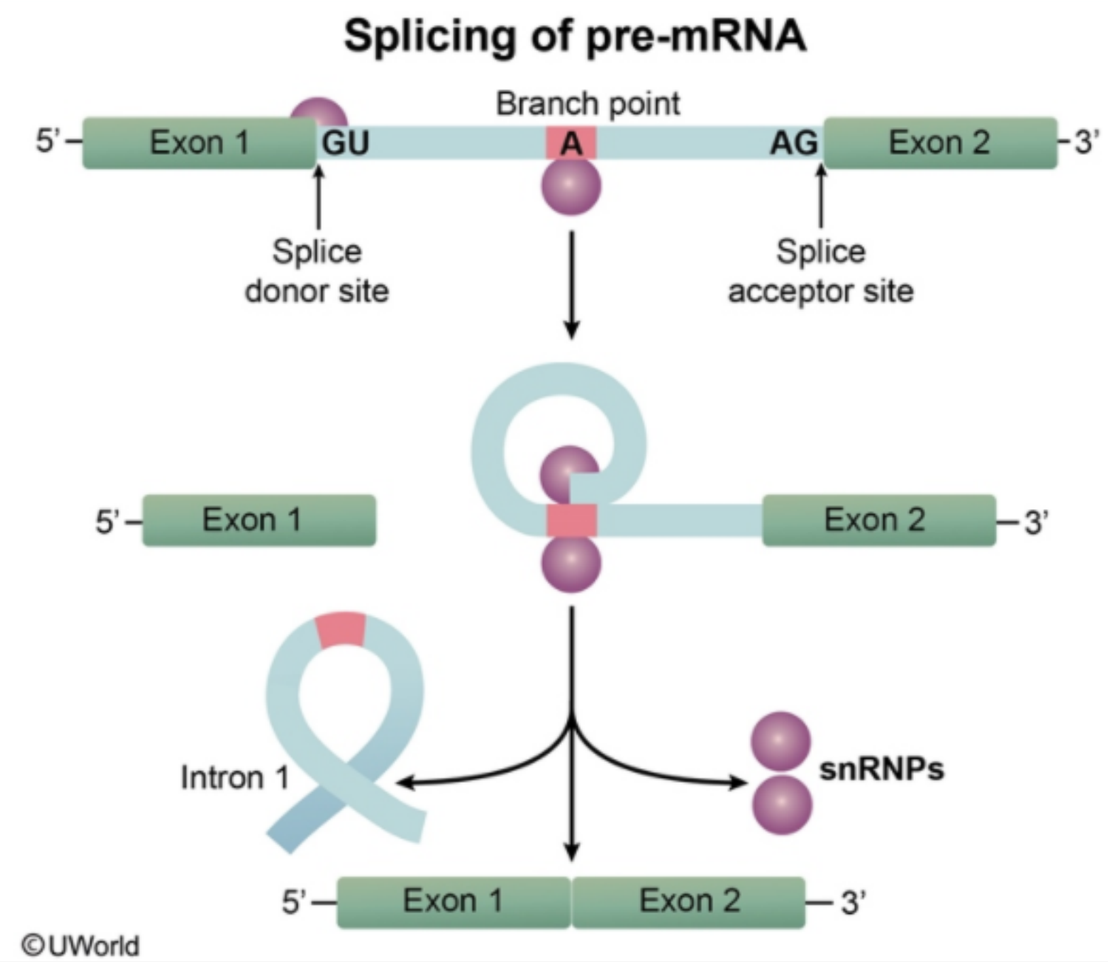
(Choice E) Ubiquitination is a process by which certain proteins are tagged with ubiquitin, a small regulatory protein, marking them for proteasomal degradation.

Educational objective:
Alternative splicing is a process by which a single gene can code for various unique proteins by selectively including or excluding different DNA coding regions (exons) into mature mRNA.

References

Alternative splicing is a process by which different combinations of DNA coding regions **(exons)** are selectively included or excluded from a

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

References

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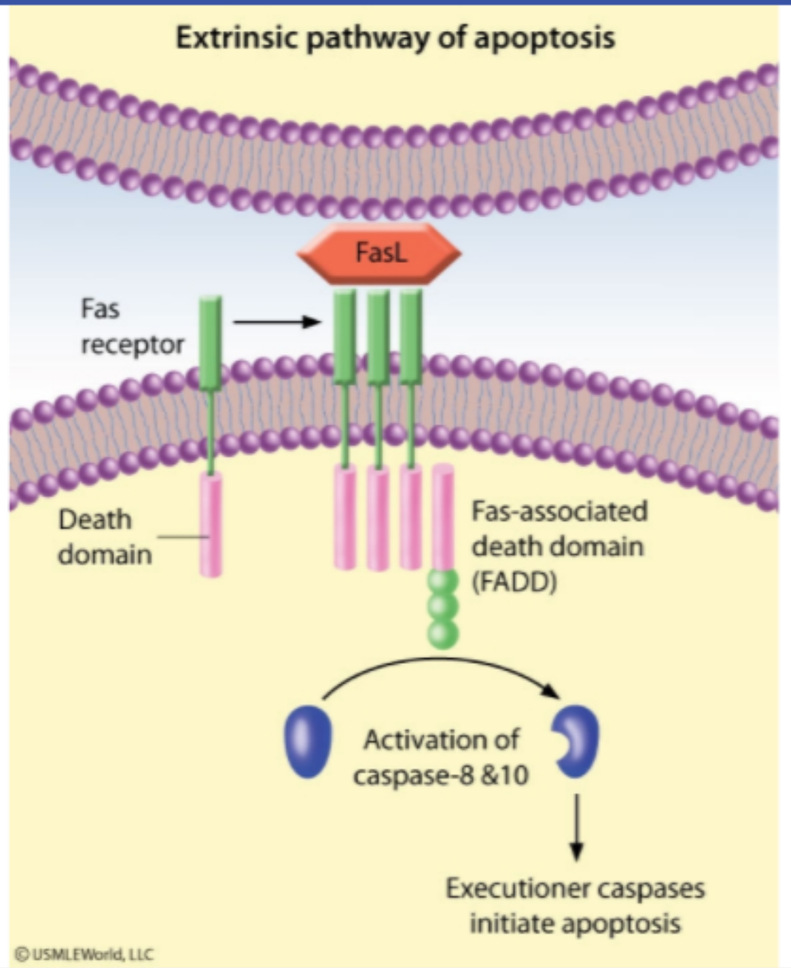
Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

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References

- Alternative pre-mRNA splicing regulation in cancer.

Genetics	General Principles	Transcription
Subject	System	Topic

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A 20-year-old man suddenly collapses while walking on a college campus. He is found to be unresponsive and pulseless by a bystander. Despite efforts by emergency medical personnel, the man is unable to be resuscitated. His friends say he appeared fatigued and described palpitations and dyspnea with exertion in the weeks leading up to the event. He had no known medical history and did not use tobacco, alcohol, or illicit drugs. The man's 3 younger siblings are healthy. His parents confirm a history of "early heart disease" in a paternal grandfather and request an autopsy and genetic testing for further evaluation. Genetic studies reveal a defect in a *TTN* gene exon resulting in a truncated titin protein. Autopsy findings are most likely to show which of the following phenotypes?

A. Arrhythmogenic right ventricular cardiomyopathy

B. Bicuspid aortic valve

C. Dilated cardiomyopathy

D. Hypertrophic cardiomyopathy

E. Restrictive cardiomyopathy

Submit

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- A. Arrhythmogenic right ventricular cardiomyopathy (8%)
- B. Bicuspid aortic valve (1%)
- ✓ C. Dilated cardiomyopathy (21%)
- D. Hypertrophic cardiomyopathy (61%)
- E. Restrictive cardiomyopathy (6%)

Omitted
Correct answer
C

21%
Answered correctly

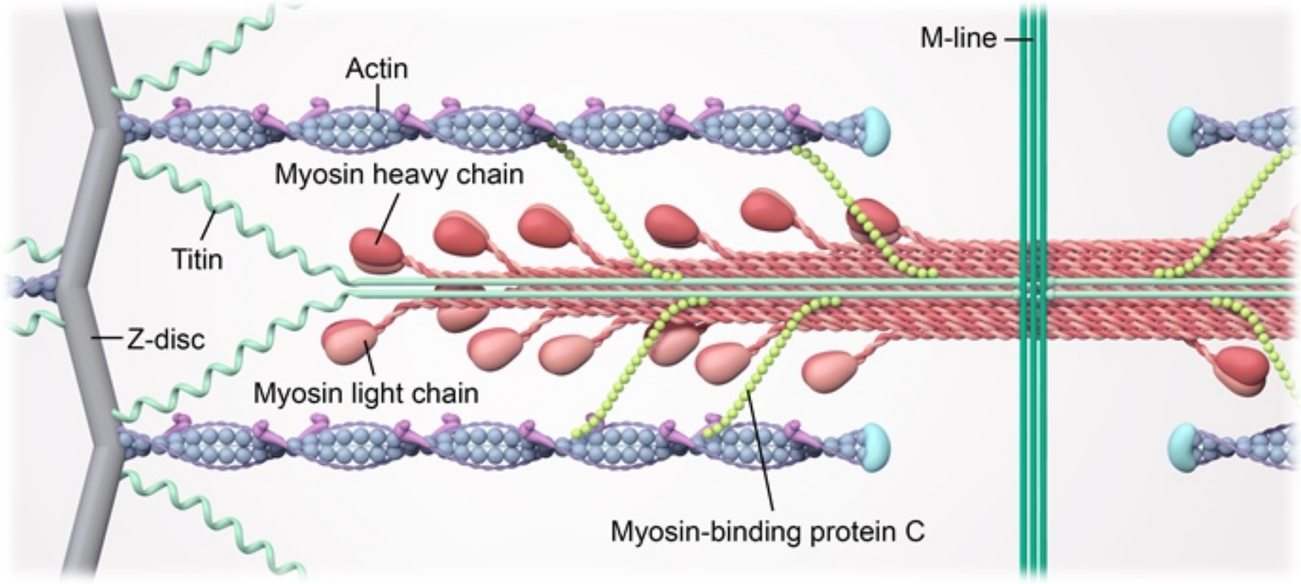
02 secs
Time Spent

01/07/2020
Last Updated

Explanation

Cardiac sarcomere protein structure

Cardiac sarcomere protein structure



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Dilated cardiomyopathy (DCM) occurs due to a direct insult to the myocardium that leads to a decrease in contractile function of one or both ventricles with a consequent increase in ventricular cavity size. It can result from a variety of causes, including viral infection, chemical toxicity (eg, doxorubicin, alcohol, cocaine), and infiltrative disease (late manifestation). Patients typically have symptoms of decompensated heart failure (eg, fatigue, dyspnea, orthopnea). In addition, the left ventricular structural changes place these patients at risk for sudden cardiac death due to ventricular arrhythmia.

Patients are classified as having **idiopathic DCM** when no apparent cause of DCM is identified on routine clinical evaluation. A large percentage of these patients likely have a **familial** (inherited) cause. Familial DCM can result from a variety of genetic mutations affecting either sarcomere (ie, the contractile apparatus) or nonsarcomere proteins. Truncating mutations (usually nonsense mutations) affecting the ***TTN* gene**, which encodes for the sarcomere protein **titin**, are the most common cause of familial DCM. Titin is an elastic protein that anchors the beta myosin

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TTN gene mutations follow **autosomal dominant** inheritance; however, they have incomplete penetrance, leading to delayed or absent clinical manifestations in some family members.

(Choice A) Arrhythmogenic right ventricular cardiomyopathy is characterized by fibrosis and scarring of right ventricular myocardium, which predisposes to ventricular arrhythmias and sudden cardiac death. The disease results from impaired desmosome function due to mutations in genes encoding desmosomal proteins (eg, plakoglobin, desmoplakin).

(Choice B) Familial bicuspid aortic valve disease has been associated with a mutation affecting the *NOTCH1* gene that encodes transcription regulatory proteins.

(Choice D) Hypertrophic cardiomyopathy is a common cause of sudden cardiac death in young patients. It is inherited in an autosomal dominant pattern and most commonly involves mutations in the genes encoding beta-myosin heavy chain or myosin-binding protein C.

(Choice E) Restrictive cardiomyopathy most commonly results from infiltrative disease (eg, amyloidosis, hemochromatosis, sarcoidosis); however, familial disease does occur. Familial restrictive cardiomyopathy typically involves mutations in genes encoding one of several sarcomere or cytoskeletal proteins, but mutations of the *TTN* gene are not a well-established cause.

Educational objective:

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Educational objective:
Autosomal dominant mutations in the *TTN* gene, which encodes for the sarcomere protein titin, are the most common cause of familial dilated cardiomyopathy.

References

- Dilated cardiomyopathy: the complexity of a diverse genetic architecture.
- Truncations of titin causing dilated cardiomyopathy

A healthy couple, who recently emigrated from Eastern Europe, bring their 3-year-old son to the office for evaluation of an eczematous rash. On examination, the child also shows signs of intellectual disability and gait abnormality and has a musty body odor. What is the likelihood that this couple's next child will be affected with the same disease?

- A. Same as the general population
- B. 1/32
- C. 1/16
- D. 1/8
- E. 1/4
- F. 1/2

Submit

A healthy couple, who recently emigrated from Eastern Europe, bring their 3-year-old son to the office for evaluation of an eczematous rash. On examination, the child also shows signs of intellectual disability and gait abnormality and has a musty body odor. What is the likelihood that this couple's next child will be affected with the same disease?

- A. Same as the general population (4%)
- B. 1/32 (0%)
- C. 1/16 (3%)
- D. 1/8 (4%)
- ✓ E. 1/4 (82%)
- F. 1/2 (4%)

Omitted
Correct answer
E

82%
Answered correctly

04 secs
Time Spent

05/18/2020
Last Updated

Explanation

Intellectual disability, gait or posture abnormality, eczema, and a musty body odor are signs of phenylketonuria (PKU). PKU is an autosomal recessive disease caused by mutation of the gene that codes for phenylalanine hydroxylase. In the United States, phenylalanine levels are measured in all neonates to screen for PKU.

Because PKU is inherited in an autosomal recessive fashion, both of the healthy parents must be heterozygous carriers of the mutation. The probability that their next child will inherit the disease is:

Omitted
Correct answer
E

82%
Answered correctly

04 secs
Time Spent

05/18/2020
Last Updated

Explanation

Intellectual disability, gait or posture abnormality, eczema, and a musty body odor are signs of phenylketonuria (PKU). PKU is an autosomal recessive disease caused by mutation of the gene that codes for phenylalanine hydroxylase. In the United States, phenylalanine levels are measured in all neonates to screen for PKU.

Because PKU is inherited in an autosomal recessive fashion, both of the healthy parents must be heterozygous carriers of the mutation. The probability that their next child will inherit the disease is:

p_1 = probability that the mother transmits the mutant allele = 1/2
p_2 = probability that the father transmits the mutant allele = 1/2

The probability that a child will inherit a mutant allele from each carrier parent is equal to $p_1 \times p_2 = 1/4$, as these are independent events.

Educational objective:
Intellectual disability, gait or posture abnormality, eczema, and a musty body odor in a toddler are signs of phenylketonuria (PKU). Most infants with PKU are born to 2 heterozygous carrier parents. The probability that heterozygous carrier parents will transmit an autosomal recessive disease such as PKU to a child is 1/4.

Genetics	Endocrine, Diabetes & Metabolism	Phenylketonuria
Subject	System	Topic

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A pharmaceutical researcher performs preclinical testing on a novel chemotherapeutic drug. When rat embryos are exposed to this drug during an early stage of organogenesis, they develop severe skeletal malformations. Further genetic analysis reveals that the drug causes mutations in numerous homeobox genes containing highly conserved 180 base pair DNA sequences. The genes affected by this drug most likely code for which of the following proteins?

- A. Cell surface receptors
- B. Cytoplasmic enzymes
- C. DNA replication enzymes
- D. Structural proteins
- E. Transcription regulators
- F. Transport proteins

Submit

A pharmaceutical researcher performs preclinical testing on a novel chemotherapeutic drug. When rat embryos are exposed to this drug during an early stage of organogenesis, they develop severe skeletal malformations. Further genetic analysis reveals that the drug causes mutations in numerous homeobox genes containing highly conserved 180 base pair DNA sequences. The genes affected by this drug most likely code for which of the following proteins?

- A. Cell surface receptors (4%)
- B. Cytoplasmic enzymes (1%)
- C. DNA replication enzymes (8%)
- D. Structural proteins (25%)
- ✓ E. Transcription regulators (56%)
- F. Transport proteins (3%)

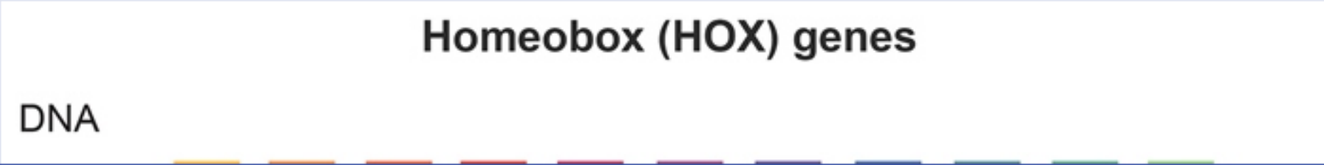
Omitted
Correct answer
E

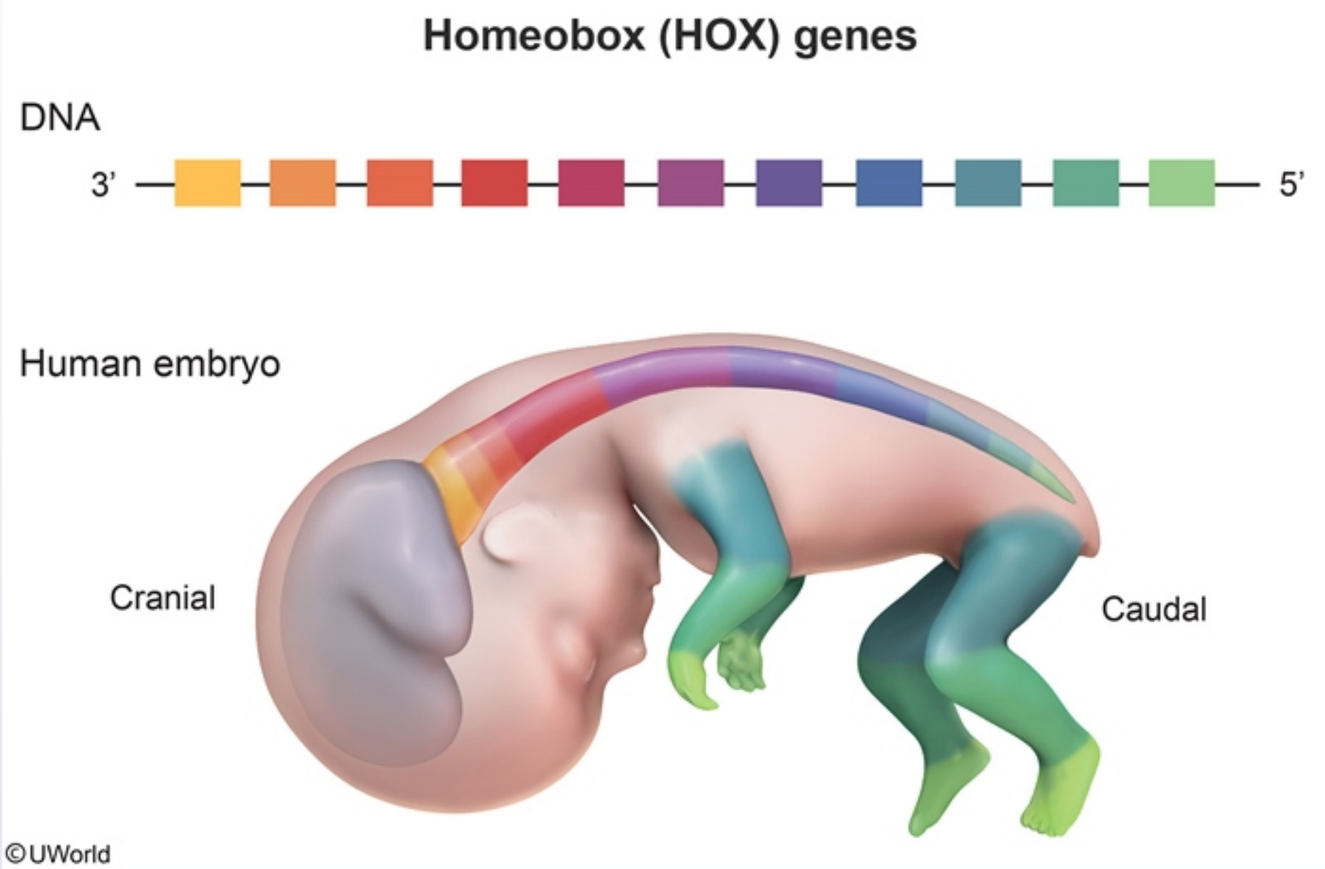
56%
Answered correctly

02 secs
Time Spent

02/09/2020
Last Updated

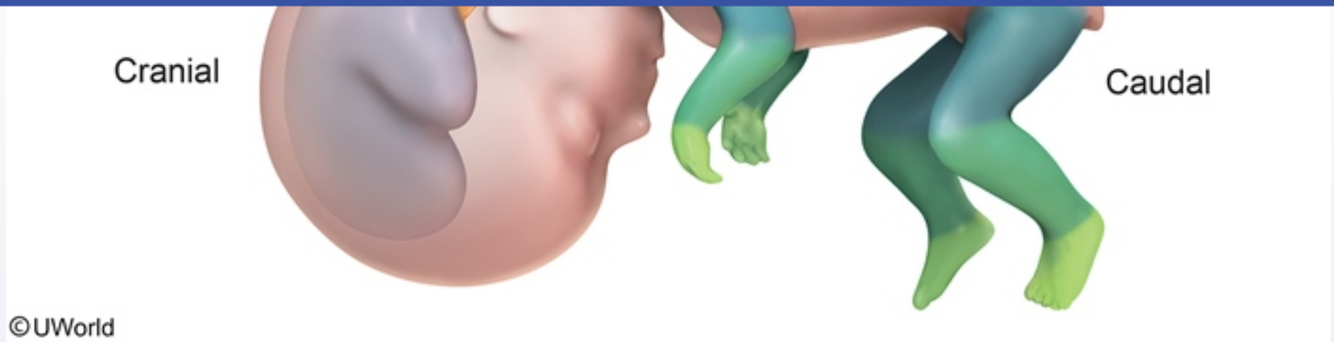
Explanation





A homeobox is a highly conserved DNA sequence that is usually about 180 nucleotides in length. A gene containing a homeobox sequence is called a **homeobox** or **hox gene**. These genes typically code for **transcription factors** that bind to regulatory regions on DNA, altering the expression of genes involved in the segmental organization of the embryo. Proper morphogenesis ensures that tissues, organs, and structural elements of the body are formed in the correct position along the cranio-caudal axis. Homeobox gene mutations interrupt this developmental process, often resulting in severe abnormalities such as skeletal malformations and improperly positioned limbs and appendages.

(Choices A, B, C, D, and E) Homeobox genes do not typically encode cell surface receptors, cytoplasmic enzymes, DNA replication enzymes



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(Choices A, B, C, D, and F) Homeobox genes do not typically encode cell surface receptors, cytoplasmic enzymes, DNA replication enzymes, structural proteins, or transport proteins.

Educational objective:
Homeobox genes encode DNA-binding transcription factors that play an important role in the segmental organization of the embryo along the cranio-caudal axis.

References

- The regulation of Hox gene expression during animal development.

Genetics	General Principles	Transcription
Subject	System	Topic

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A 5-year-old girl is brought to the office by her mother because she is concerned that her daughter "sunburns too easily." The mother says the patient's skin becomes red and scaly with only minimal sun exposure. She first noticed the problem when her daughter was 7 months old during a trip to the beach. The mother has since avoided exposing her child to excess sunlight, but finds it difficult now that the patient has begun kindergarten. Physical examination shows thin and hyperpigmented skin. She also has a few nevi on her hands that have been enlarging rapidly. This patient's disorder is most likely due to a primary defect involving which of the following processes?

- A. DNA mismatch repair
- B. Nucleotide excision repair
- C. Ras signal transduction
- D. Regulation of apoptosis
- E. Regulation of cell cycle
- F. Repair of DNA crosslinks

Submit

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- A. DNA mismatch repair (10%)
- ✓ B. Nucleotide excision repair (71%)
- C. Ras signal transduction (1%)
- D. Regulation of apoptosis (1%)
- E. Regulation of cell cycle (1%)
- F. Repair of DNA crosslinks (13%)

Omitted
Correct answer
B

71%
Answered correctly

01 sec
Time Spent

02/26/2020
Last Updated

Explanation

This patient likely has **xeroderma pigmentosum**, a rare autosomal recessive disorder that occurs due to defective nucleotide excision repair of DNA damaged by **ultraviolet (UV) light**. Normally, the regions of DNA damaged by UV radiation are excised and replaced by a series of DNA repair enzymes. In xeroderma pigmentosum, this process is impaired and leads to the accumulation of abnormal pyrimidine nucleotides and other

Explanation

This patient likely has **xeroderma pigmentosum**, a rare autosomal recessive disorder that occurs due to defective nucleotide excision repair of DNA damaged by **ultraviolet (UV) light**. Normally, the regions of DNA damaged by UV radiation are excised and replaced by a series of DNA repair enzymes. In xeroderma pigmentosum, this process is impaired and leads to the accumulation of abnormal pyrimidine nucleotides and other carcinogenic adducts.

The skin of affected individuals is normal at birth, but they present during the first year of life with severe sun sensitivity (eg, erythema, scaling) affecting light-exposed areas, especially the face. Later, the skin shows atrophy, telangiectasias, and intermingling areas of hypo- and hyperpigmentation due to chronic UV damage. **Skin malignancies**, including malignant melanoma and squamous and basal cell carcinoma, develop as early as ages 5-6.

(Choice A) Abnormalities of genes responsible for DNA mismatch repair are found in patients with hereditary nonpolyposis colorectal cancer (HNPCC, or Lynch syndrome). These patients have a greater incidence of colorectal, endometrial, and ovarian cancer.

(Choice C) Ras codes for a G protein that regulates growth factor signal transduction. Mutations that result in a constitutively activated Ras protein cause constant and unregulated cell proliferation, leading to malignancy (particularly pancreatic and colorectal cancer).

(Choices D and E) p53 is a regulatory protein that halts cell cycle progression when DNA is damaged, allowing time for the DNA to be repaired. When the damage is irreversible, apoptosis is triggered. Acquired p53 mutations are found in the majority of spontaneous cancers, whereas inherited p53 mutations are responsible for Li-Fraumeni syndrome (which causes a wide range of malignancies at a young age).

(Choice F) Fanconi anemia is an autosomal recessive condition caused by mutations in the genes responsible for the repair of interstrand DNA crosslinks. It is the most common inherited cause of aplastic anemia and presents with short stature, absent thumbs, and increased malignancy risk.

Educational objective:
Xeroderma pigmentosum develops due to a defect in nucleotide excision repair. This disease is characterized by increased sensitivity to ultraviolet radiation and a high incidence of cutaneous malignancy.

References

- Xeroderma pigmentosum

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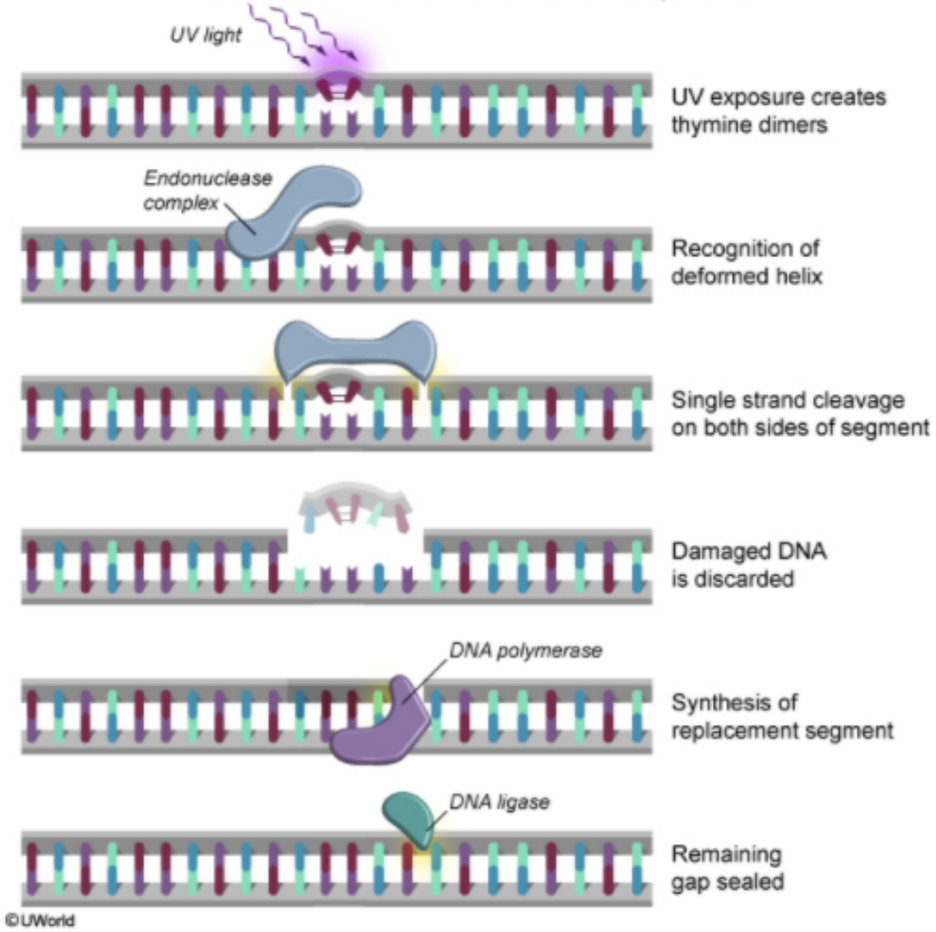
Explanation

Exhibit Display

Nucleotide excision repair of UV damaged DNA



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- Xeroderma pigmentosum

A 32-year-old woman comes to the office due to worry that she will go bald. Her father had a receding hairline with apical baldness beginning at age 20 and was completely bald by age 35. The patient's paternal grandmother and multiple other relatives on her paternal side also had early-onset baldness, but her father's siblings and the maternal side of her family have had no problems with unusual hair loss. Physical examination shows mild thinning of hair at the temporal areas, with an otherwise normal hairline, thickness, and coloration. There is no excess hair growth on her face or trunk, and she has a normal female pattern of pubic hair growth. Palpation of the thyroid is normal. Which of the following is the most likely inheritance pattern of the hair loss in this patient's family?

A. Autosomal dominant

B. Autosomal recessive

C. Mitochondrial

D. Polygenic

E. Sporadic

Submit

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- A. Autosomal dominant (19%)
- B. Autosomal recessive (23%)
- C. Mitochondrial (7%)
- ✓ D. Polygenic (45%)
- E. Sporadic (4%)

Omitted
Correct answer
D

45%
Answered correctly

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01/12/2020
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Explanation

Common medical conditions with polygenic inheritance

Common medical conditions with polygenic inheritance
• Androgenetic alopecia • Epilepsy • Glaucoma • Hypertension • Ischemic heart disease • Schizophrenia • Type II diabetes mellitus

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The most common type of hair loss in males and females is **androgenetic alopecia** (male pattern baldness). As the name implies, the hair loss is driven by both hormonal (eg, circulating androgens) and genetic factors. The hair loss occurs primarily at the temporal areas and vertex and progresses through life. The pattern and severity vary between males and females.

Androgenetic alopecia demonstrates **polygenic inheritance** with variable expressivity. Key sites of genetic influence have been identified on the short arm of chromosome 20, and also on the X and possibly Y chromosomes. Therefore, some of the genetic factors may be transmitted with X-linked recessive inheritance (eg, gene variations in the androgen receptor), whereas others will show autosomal dominant inheritance **(Choice A)**.

(Choice B) Autosomal recessive inheritance classically shows disease development in 25% of offspring from 2 asymptomatic carrier parents. In most cases, conditions with autosomal recessive inheritance will not be seen in consecutive generations.

(Choice C) Conditions passed through mitochondrial inheritance are transmitted only by the mother, and all of her offspring are affected. Conditions transmitted by mitochondrial inheritance include a number of uncommon neuromuscular disorders.

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(Choice C) Conditions passed through mitochondrial inheritance are transmitted only by the mother, and all of her offspring are affected. Conditions transmitted by mitochondrial inheritance include a number of uncommon neuromuscular disorders.

(Choice E) By definition, sporadic cases do not follow an inheritance pattern. Sporadic cases occur haphazardly among unrelated members of a population over time. For example, there may be a spontaneous gene mutation that causes a sporadic disorder in an individual with no family history of the disease.

Educational objective:
Androgenetic alopecia is the most common cause of hair loss in both males and females. The pattern and severity of the baldness depend on both hormonal (circulating androgens) and genetic factors and vary between males and females. The condition is polygenic with variable expressivity.

References

- Genetic variation in the human androgen receptor gene is the major determinant of common early-onset androgenetic alopecia.
- Male-pattern baldness susceptibility locus at 20p11.

Genetics	Dermatology	Hair loss
Subject	System	Topic

Researchers lyse human cells and isolate a specific messenger RNA template using gel electrophoresis. Reverse transcription polymerase chain reaction is then used to synthesize complementary DNA (cDNA) from the RNA template. Next, the cDNA is modified into an expression vector containing an optimized bacterial promoter, ribosomal binding site, and terminator sequence. After insertion of the vector into appropriate bacterial hosts, the transformed bacteria are cultured in a bioreactor and produce large quantities of a protein containing a domain that binds to a specific DNA sequence. This protein is most likely the receptor for which of the following hormones?

- A. Glucagon
- B. Growth hormone
- C. Insulin
- D. Insulin-like growth factor
- E. Parathyroid hormone
- F. Progesterone

Submit

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A. Glucagon (2%)
B. Growth hormone (12%)
C. Insulin (11%)
D. Insulin-like growth factor (14%)
E. Parathyroid hormone (2%)
✓ F. Progesterone (56%)

Omitted
Correct answer
F

56%
Answered correctly

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02/08/2020
Last Updated

Explanation

Intracellular receptors | **Surface receptors**

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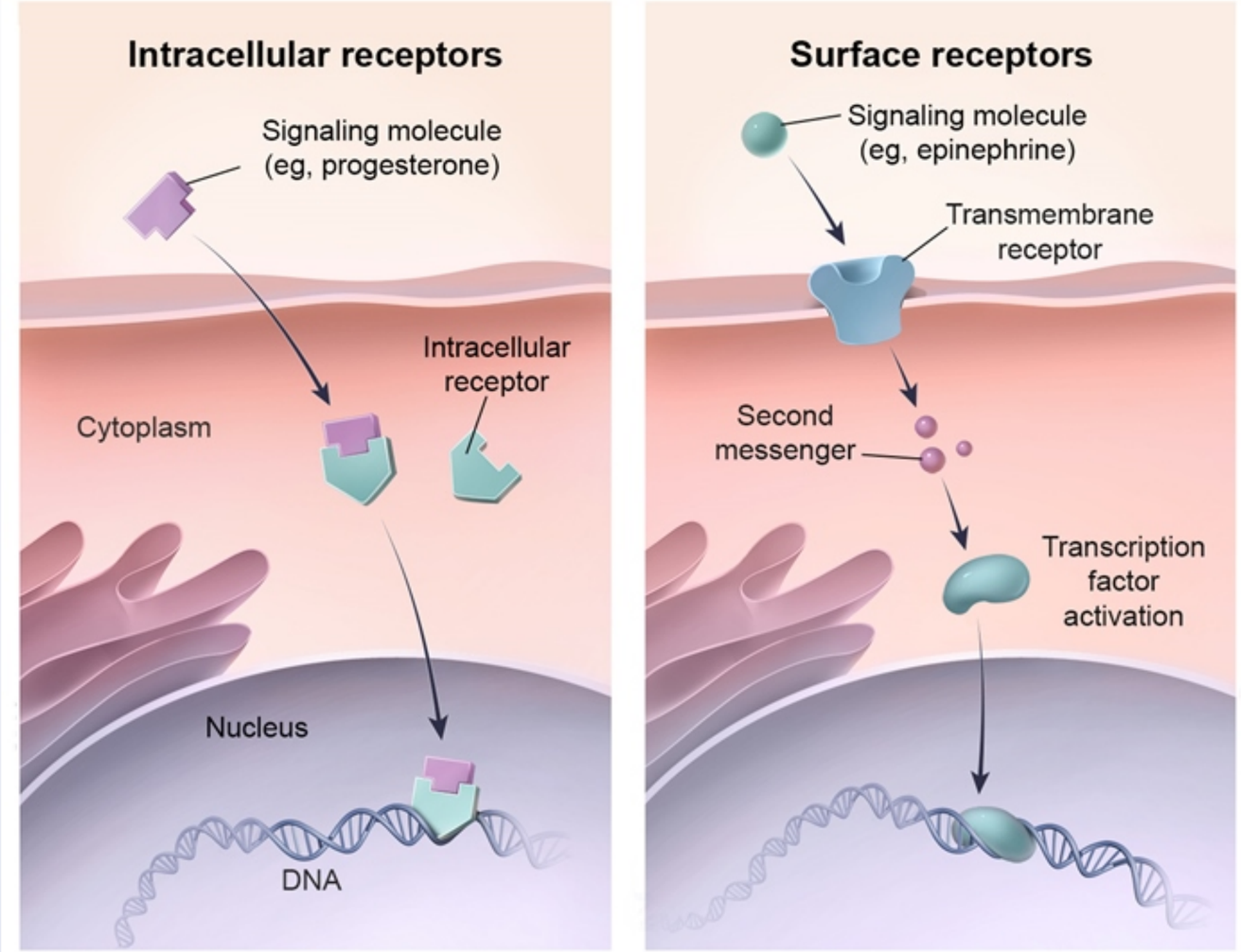

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Prokaryotes and eukaryotes use divergent cellular machinery for protein synthesis and require different signaling sequences for efficient transcription and translation. Expression cloning is a type of DNA cloning where the signals necessary for optimal protein expression are included

Prokaryotes and eukaryotes use divergent cellular machinery for protein synthesis and require different signaling sequences for efficient transcription and translation. Expression cloning is a type of DNA cloning where the signals necessary for optimal protein expression are included in the DNA vector. In this example, **eukaryotic complementary DNA** (containing the **coding sequence** for the protein of interest) is modified with **prokaryotic promoter** sequences (eg, the Pribnow box, −35 sequence) and a **ribosomal binding site** (Shine-Dalgarno sequence). The vector is then incorporated into a suitable bacterial host (eg, *Escherichia coli*) and subsequently transcribed and translated into protein.

The protein produced in the bioreactor contains a **DNA-binding domain**. DNA-binding proteins are a diverse group that include **transcription factors** (Myc, CREB), **steroid** receptors (cortisol, aldosterone, progesterone), **thyroid hormone** receptor, **fat-soluble vitamin receptors** (vitamin D, retinoic acid), and DNA transcription and replication proteins.

Of the choices listed, only the **progesterone receptor** can bind to DNA. The receptors for most steroid hormones, including progesterone, are located in the cytoplasm and translocate to the nucleus upon ligand binding. In contrast, receptors for thyroid hormone and vitamins A and D are located within the nucleus at all times. Following activation by ligand binding, both receptor types attach to DNA at hormone response elements located in the promoter region of target genes to alter gene transcription.

(Choices A and E) Parathyroid hormone and glucagon act on Gs protein-coupled receptors found on the cell membrane. Binding their respective ligands subsequently activates adenylyl cyclase and increases intracellular cyclic AMP concentration.

(Choice B) Growth hormone receptor is a membrane-bound receptor that works via activating the JAK-STAT pathway.

(Choices C and D) The receptors for insulin-like growth factor-1 (IGF-1) and insulin are structurally similar and located at the cell membrane. The intracellular domains of these receptors have intrinsic tyrosine kinase activity, which is activated on ligand binding. Autophosphorylation of the tyrosine residues on the intracellular part of the receptors then triggers downstream signaling.

Educational objective:
DNA-binding proteins include transcription factors (Myc, CREB), steroid receptors (cortisol, aldosterone, progesterone), thyroid hormone receptor, fat-soluble vitamin receptors (vitamin D, retinoic acid), and DNA transcription and replication proteins.

References

- Steroid hormone receptors: interaction with deoxyribonucleic acid and transcription factors.

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Genetics	General Principles	Transcription
Subject	System	Topic

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Electron microscopy of a eukaryotic cell during interphase of the cell cycle shows 10-nm thick chromatin fibers with a "beads on a string" appearance. These chromatin fibers are extracted and treated with an endonuclease, which preferentially cleaves the "string" portions of the chromatin. Further evaluation of the "beads" reveals that they are composed of DNA wrapped around a core of proteins. Which of the following proteins is most likely found outside of this core and helps promote chromatin compaction?

A. Histone H1
B. Histone H3
C. Histone H4
D. snRNP
E. Topoisomerase II
F. Ubiquitin

Submit

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- ✓ A. Histone H1 (73%)
- B. Histone H3 (6%)
- C. Histone H4 (11%)
- D. snRNP (2%)
- E. Topoisomerase II (3%)
- F. Ubiquitin (2%)

Omitted
Correct answer
A

73%
Answered correctly

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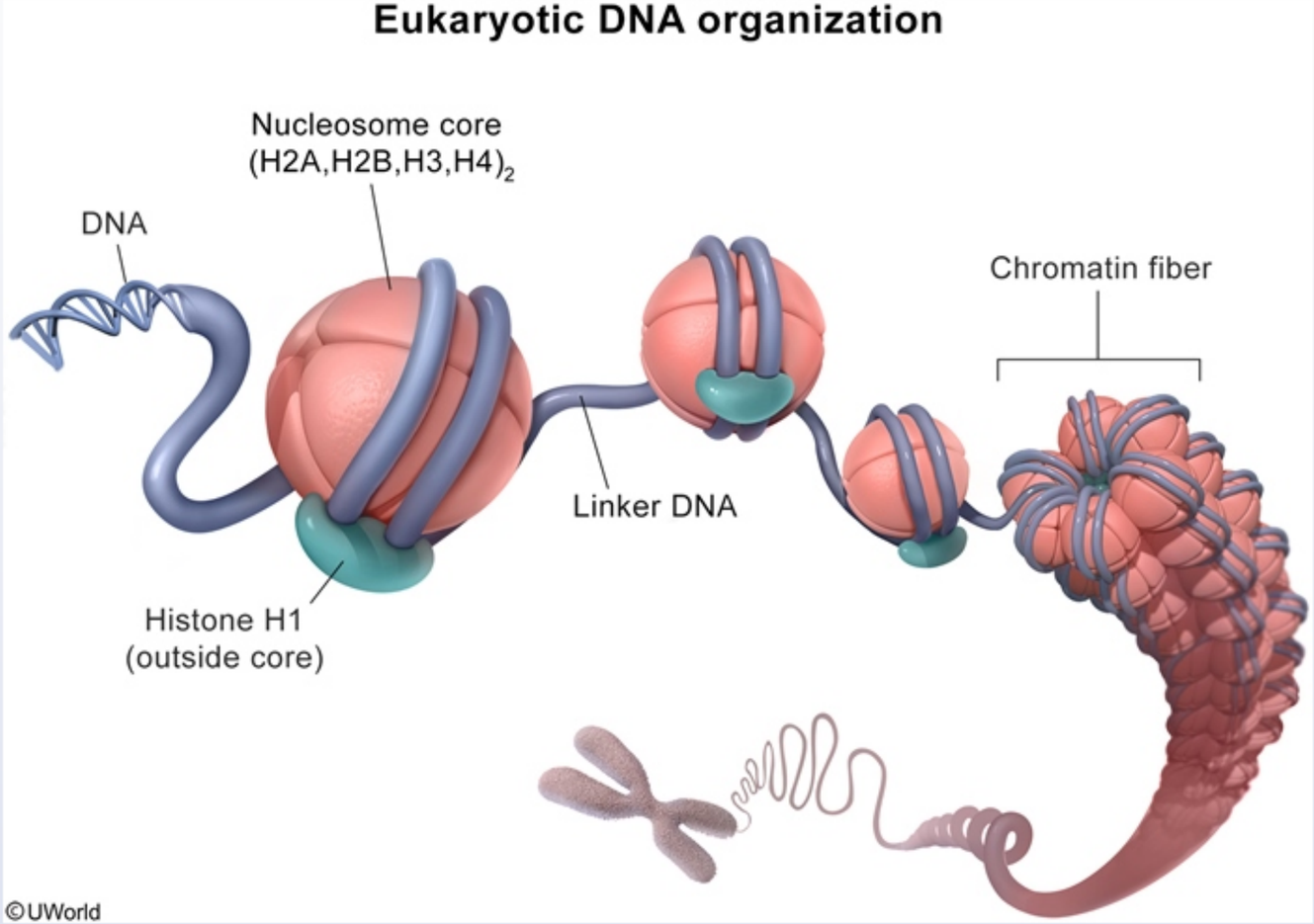
03/03/2020
Last Updated

Explanation

Eukaryotic DNA organization

Nucleosome core
(H2A, H2B, H3, H4)



Nucleosomes are structural subunits within the nucleus of eukaryotic cells that are composed of DNA wrapped around a core of histone proteins. There are 5 major subtypes of histones: H1, H2A, H2B, H3, and H4. Each histone core is made up of 8 histone proteins: 2 molecules each of H2A, H2B, H3, and H4 **(Choices B and C)**. During the initial steps of DNA packaging into chromatin, the negatively charged DNA double helix wraps around the positively charged histone core twice.

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In contrast to the other histone proteins, **H1** is located **outside** of the **histone core**. H1 histones bind the **linker** segments of DNA that lie between nucleosomes and facilitate **packaging of nucleosomes** into more compact structures. DNA associated with histones has the appearance of "beads on a string." This structure undergoes further rounds of coiling and associates with other proteins (eg, nuclear scaffold protein), ultimately forming chromosomes.

(Choice D) Small nuclear ribonucleoproteins (snRNPs) help to splice out introns from pre-mRNA, forming mature mRNA.

(Choice E) During prokaryotic DNA replication, topoisomerase II (DNA gyrase) relieves the tension created during DNA strand unwinding by introducing negative supercoils into the DNA.

(Choice F) Ubiquitin is a small protein present in the cytoplasm and nucleus of all eukaryotes. It is typically covalently attached to various intracellular proteins to signal for their degradation by the proteasome (ubiquitin-proteasome pathway).

Educational objective:
Nucleosomes are composed of DNA wrapped around a core of 8 histone proteins (2 molecules each of H2A, H2B, H3, and H4). H1 histone is located outside of this histone core and helps package nucleosomes into more compact structures by binding and linking the DNA between adjacent nucleosomes.

References

- H1 histones: current perspectives and challenges.

Genetics	General Principles	Dna structure & function
Subject	System	Topic

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A 2-month-old boy is brought to the emergency department due to progressively worsening "floppiness" and poor feeding. The infant was born in Eastern Europe via an uncomplicated vaginal delivery to a 38-year-old woman and then immigrated to the United States with his family. The parents describe the infant as a "good baby" who rarely cries and sleeps through the night but has lately been difficult to rouse for breastfeeding. Stools have also decreased to every other day and are small and pellet-like. Physical examination shows a hypotonic infant with a large anterior fontanelle, large tongue, and a reducible umbilical hernia. He has low tone and is unable to hold his head erect on his own. No other abnormalities are seen. Which of the following is the most likely cause of this patient's condition?

- A. Botulism
- B. Down syndrome
- C. Galactosemia
- D. Hirschsprung disease
- E. Hypothyroidism
- F. Phenylketonuria

Submit

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- A. Botulism (20%)
- B. Down syndrome (11%)
- C. Galactosemia (10%)
- D. Hirschsprung disease (5%)
- ✓ E. Hypothyroidism (41%)
- F. Phenylketonuria (9%)

Omitted
Correct answer
E

41%
Answered correctly

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Explanation

Congenital hypothyroidism

Congenital hypothyroidism	

Clinical manifestations	• Initially normal at birth
	• Symptoms develop after maternal T_4 wanes:
	  ◦ Lethargy
	  ◦ Enlarged fontanelle
	  ◦ Protruding tongue
	  ◦ Umbilical hernia
	  ◦ Poor feeding
	  ◦ Constipation
	  ◦ Dry skin
	  ◦ Jaundice

Diagnosis	• ↑ TSH & ↓ free T_4 levels • Newborn screening
Treatment	• Levothyroxine

Congenital hypothyroidism is one of the most common causes of preventable intellectual disability. Most cases are due to thyroid dysgenesis (agenesis, hypoplasia, or ectopy), and iodine deficiency is a common cause in areas endemic for iodine deficiency (eg, Europe).

Neonates initially have no significant symptoms due to the presence of maternal thyroxine (T_4) from transplacental transfer. T_4 is responsible for the stimulation of protein synthesis as well as carbohydrate and lipid catabolism in many cells; as maternal T_4 wanes, metabolism is impaired and marked by a slowing of physical and mental activity (lethargy, poor feeding, constipation, hypotonia). Accumulation of matrix substances cutaneously and internally results in nonpitting edema (eg, "**puffy**" face), umbilical hernia, protruding tongue, and a large anterior fontanelle. In addition, T_4 is essential for normal brain development and myelination during early life, and infants are at risk of severe and **irreversible intellectual disability**.

Treatment with **levothyroxine** by age 2 weeks can normalize cognitive and physical development.

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Treatment with **levothyroxine** by age 2 weeks can normalize cognitive and physical development.

Therefore, universal newborn screening for congenital hypothyroidism is performed in the United States but not in all other countries.

(Choice A) Infants who are fed honey or exposed to spores from the soil are at risk for infantile botulism, which presents with constipation and flaccid paralysis. A large anterior fontanelle, umbilical hernia, and macroglossia are not seen.

(Choice B) Hypotonia and hypothyroidism are features of Down syndrome. However, the absence of other dysmorphic features (eg, upslanting palpebral fissures, bilateral epicanthal folds, single palmar crease) makes Down syndrome unlikely in this patient.

(Choice C) Galactosemia is caused by galactose-1-phosphate uridyltransferase deficiency. Patients with this condition present with jaundice, vomiting, hepatomegaly, and lethargy after ingesting galactose in breast milk or formula in the first few days of life. This patient was previously breastfeeding well and has no hepatomegaly.

(Choice D) Hirschsprung disease is caused by abnormal migration of neural crest cells into the rectosigmoid colon. The lack of ganglion cells in this colon segment impedes gastrointestinal motility, resulting in failed meconium passage and bilious emesis in a newborn.

(Choice F) Phenylketonuria is most commonly caused by phenylalanine hydroxylase deficiency, resulting in hyperphenylalaninemia. It presents with developmental delay, light pigmentation, and a musty body odor.

Educational objective:
Congenital hypothyroidism is usually asymptomatic at birth. After maternal T_4 wanes, infants develop constipation, lethargy, hypotonia,

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Educational objective:
Congenital hypothyroidism is usually asymptomatic at birth. After maternal T_4 wanes, infants develop constipation, lethargy, hypotonia, macroglossia, an umbilical hernia, and a large anterior fontanelle.

References

- Newborn screening for congenital hypothyroidism.
- Update of newborn screening and therapy for congenital hypothyroidism.
- Thyroid-related neurological disorders and complications in children.

Genetics	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

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(agenesis, hypoplasia, or ectopy), and iodine deficiency is a common cause in areas endemic for iodine deficiency (eg, Europe).

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Therefore, universal newb

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Educational objective:
Congenital hypothyroidism
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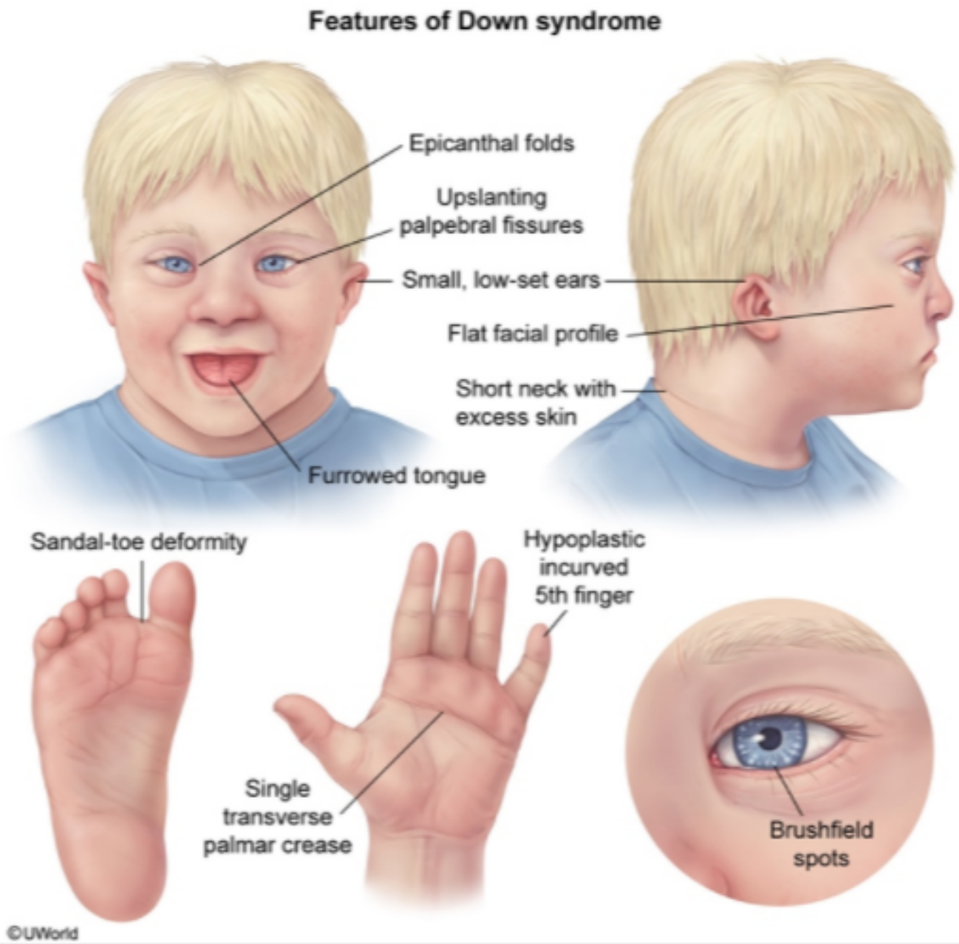

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A pharmaceutical researcher develops a new drug that affects bacterial protein synthesis. In an experiment, *Escherichia coli* is exposed to the drug and serially cultured in media containing tagged nucleotides and amino acids. It is found that the drug inhibits molecules that recognize the highlighted codon in the bacterial mRNA fragment shown in the image below.

5' --- ACG CUA CCA UUG CAA GUU AGC UAA AUA GCG UUC --- 3'

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Which of the following molecules is the most likely target of this drug?

- A. Charged tRNA
- B. Elongation factor 2
- C. Releasing factor 1
- D. snRNP
- E. Transcription factor II D
- F. Uncharged tRNA

Submit

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Which of the following molecules is the most likely target of this drug?

- A. Charged tRNA (15%)
- B. Elongation factor 2 (7%)
- ✓ C. Releasing factor 1 (56%)
- D. snRNP (5%)
- E. Transcription factor II D (3%)
- F. Uncharged tRNA (12%)

Omitted
Correct answer
C

56%
Answered correctly

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Explanation

There are 64 codons in the genetic code, the majority of which code for amino acids. However, because there are only 20 amino acids, most have more than one codon. For example, GUU, GUC, GUA, and GUG all code for valine.

In addition, there are codons that call for initiation or **termination of protein synthesis**. The universal start codon is AUG, which codes for methionine. **UAA, UAG**, and **UGA** are **stop codons**, which do not code for amino acids or bind tRNA. Instead, when the ribosome encounters a stop codon, **releasing factor** proteins bind to the ribosome and stimulate release of the formed polypeptide chain and dissolution of the ribosome-mRNA complex.

(Choice A) Charged tRNA delivers amino acids to the protein synthesis complex. The anticodon on a tRNA molecule recognizes the corresponding codon on mRNA, assuring proper amino acid sequencing.

(Choice B) Elongation factors facilitate tRNA binding and the translocation steps of protein synthesis.

(Choice D) Transcription produces a pre-mRNA molecule containing both introns and exons. Splicing is a post-transcriptional modification in which introns are removed from pre-mRNA via small nuclear ribonucleoproteins (snRNPs).

(Choice E) Initiation of gene transcription is governed by the binding of transcription factors to the regulatory region of the gene. Transcription factor II D binds to the TATA promoter sequence located ~25 bases upstream from the coding region of the gene.

(Choice F) During protein synthesis, uncharged tRNA (lacking an amino acid) does not interact with mRNA and ribosomes.

Educational objective:
Releasing factors recognize stop codons (eg, UAA, UAG, and UGA) and terminate protein synthesis. They facilitate release of the polypeptide chain from the ribosome and dissolution of the ribosome-mRNA complex.

References

- Terminating eukaryote translation: domain 1 of release factor eRF1 functions in stop codon recognition.
- Two-step model of stop codon recognition by eukaryotic release factor eRF1.

Genetics General Principles Translation

A 1-day-old infant in the newborn nursery is found to have a harsh, holosystolic murmur on physical examination. The neonate was born at 39 weeks gestation to a 36-year-old woman who opted to defer prenatal screening. Review of medical records shows no family history of genetic or chromosomal disorders. The infant's vital signs are appropriate for his age. The rest of the physical examination shows a flat facial profile, protruding tongue, and small ears. Which of the following most likely occurred prior to conception?

- A. Chromosomal deletion
- B. Chromosomal translocation
- C. Gene inactivation
- D. Meiotic nondisjunction
- E. Trinucleotide repeat expansion

Submit

A 1-day-old infant in the newborn nursery is found to have a harsh, holosystolic murmur on physical examination. The neonate was born at 39 weeks gestation to a 36-year-old woman who opted to defer prenatal screening. Review of medical records shows no family history of genetic or chromosomal disorders. The infant's vital signs are appropriate for his age. The rest of the physical examination shows a flat facial profile, protruding tongue, and small ears. Which of the following most likely occurred prior to conception?

- A. Chromosomal deletion (5%)
- B. Chromosomal translocation (5%)
- C. Gene inactivation (1%)
- ✓ D. Meiotic nondisjunction (84%)
- E. Trinucleotide repeat expansion (3%)

Omitted
Correct answer
D

84%
Answered correctly

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03/24/2020
Last Updated

Explanation

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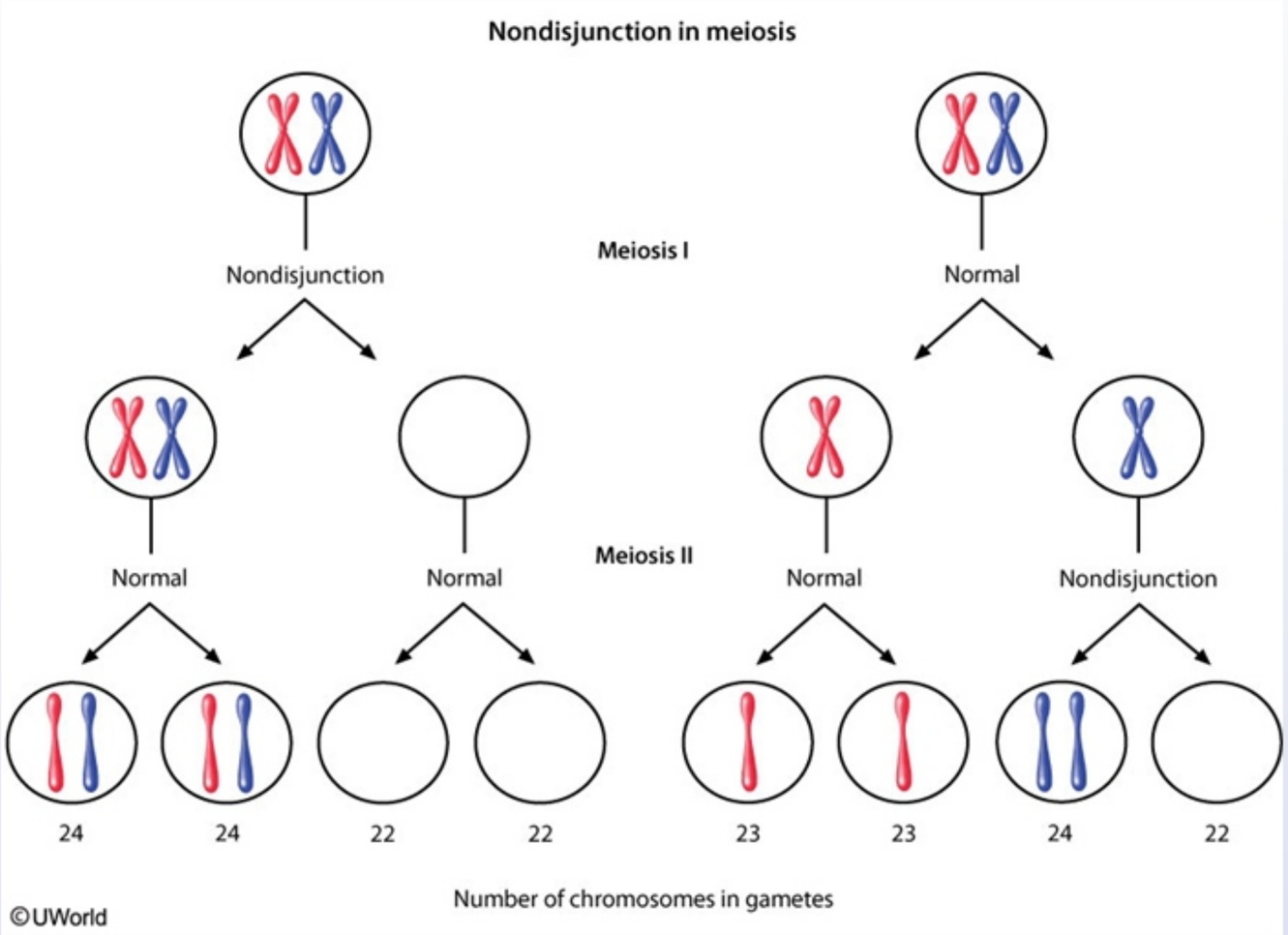

During normal meiosis, homologous chromosomes separate to pass on individual chromatids to daughter cells. In **meiotic nondisjunction**, the chromosomes fail to separate, allowing one or more daughter cells to pass on with an **extra copy** of a chromosome. Increasing maternal age, particularly **age ≥35**, is associated with an elevated risk of nondisjunction that is likely due to cumulative oxidative stress, depletion of available

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During normal meiosis, homologous chromosomes separate to pass on individual chromatids to daughter cells. In **meiotic nondisjunction**, the chromosomes fail to separate, allowing one or more daughter cells to pass on with an **extra copy** of a chromosome. Increasing maternal age, particularly **age ≥35**, is associated with an elevated risk of nondisjunction that is likely due to cumulative oxidative stress, depletion of available mature oocytes, and shortening of oocyte telomeres. From highest to lowest prevalence, the most common consequences of maternal nondisjunction are **trisomies 21** (Down syndrome), 18 (Edwards syndrome), and 13 (Patau syndrome).

Less than 5% of Down syndrome cases are caused by a Robertsonian translocation **(Choice B)**, which results from a break near the centromeres of 2 chromosomes (eg, chromosomes 14 and 21) and subsequent transfer of genetic material between these chromosomes. This translocation results in 46 chromosomes in the fetus with 3 effective copies of chromosome 21.

Classic features of Down syndrome include a flat facial profile, epicanthal folds, upslanting palpebral fissures, protruding tongue, and small ears. Congenital heart defects (eg, complete atrioventricular defect, ventricular or atrial septal defect) are seen in 50% of patients.

(Choice A) Chromosomal deletions are associated with cri-du-chat syndrome (5p deletion), DiGeorge syndrome (22q11 microdeletion), and Prader-Willi syndrome (15q deletion). Deletions are not associated with increased maternal age.

(Choice C) Imprinting is the selective inactivation of a maternal or paternal allele. When a selectively expressed allele is abnormal (eg, gene deletion), conditions such as Prader-Willi syndrome (maternal inactivation/paternal deletion) or Angelman syndrome (paternal inactivation/maternal deletion) can result.

(Choice E) Trinucleotide repeat expansions within DNA can dysregulate protein production, causing disorders such as Huntington disease, myotonic dystrophy, and fragile X syndrome.

Educational objective:
Down syndrome is most commonly caused by maternal meiotic nondisjunction, a process by which the fetus receives 3 full copies of chromosome 21. Dysmorphic features (eg, flat facial profile, protruding tongue, small ears, upslanting palpebral fissures) and cardiac defects (eg, endocardial cushion defects) are characteristic.

References

- Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down

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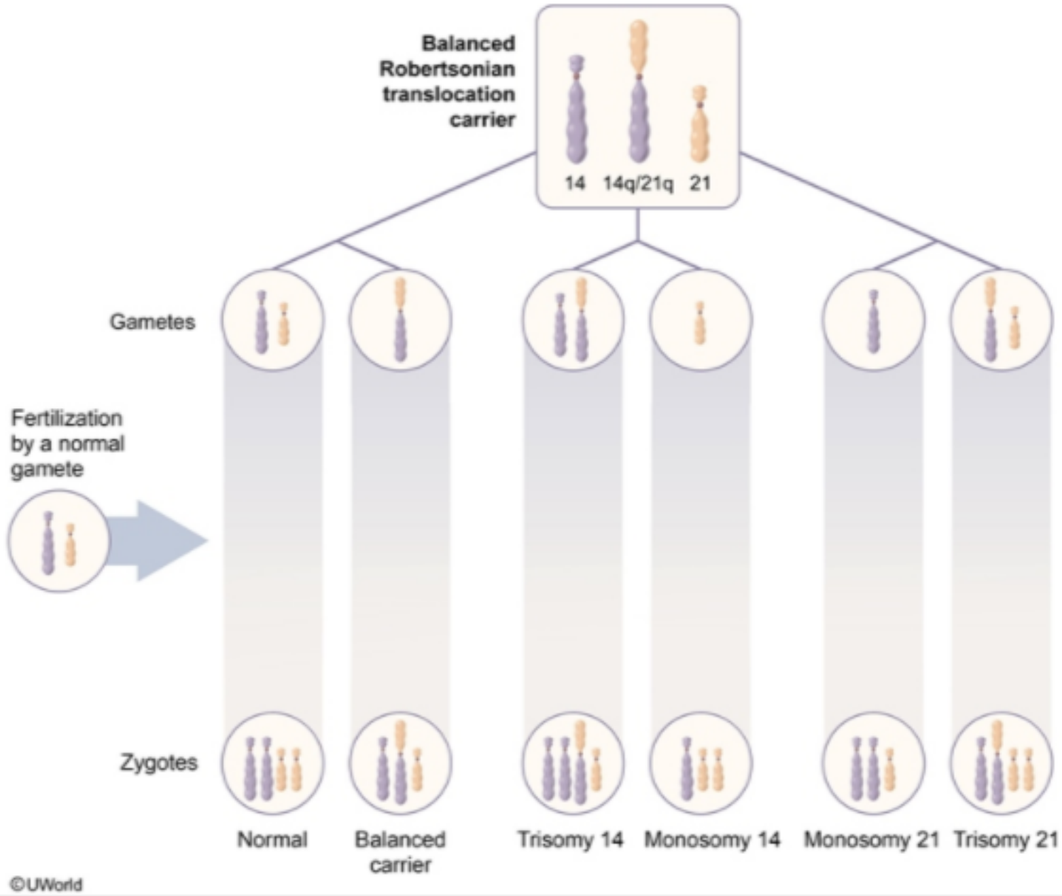
Robertsonian translocation



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- Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down

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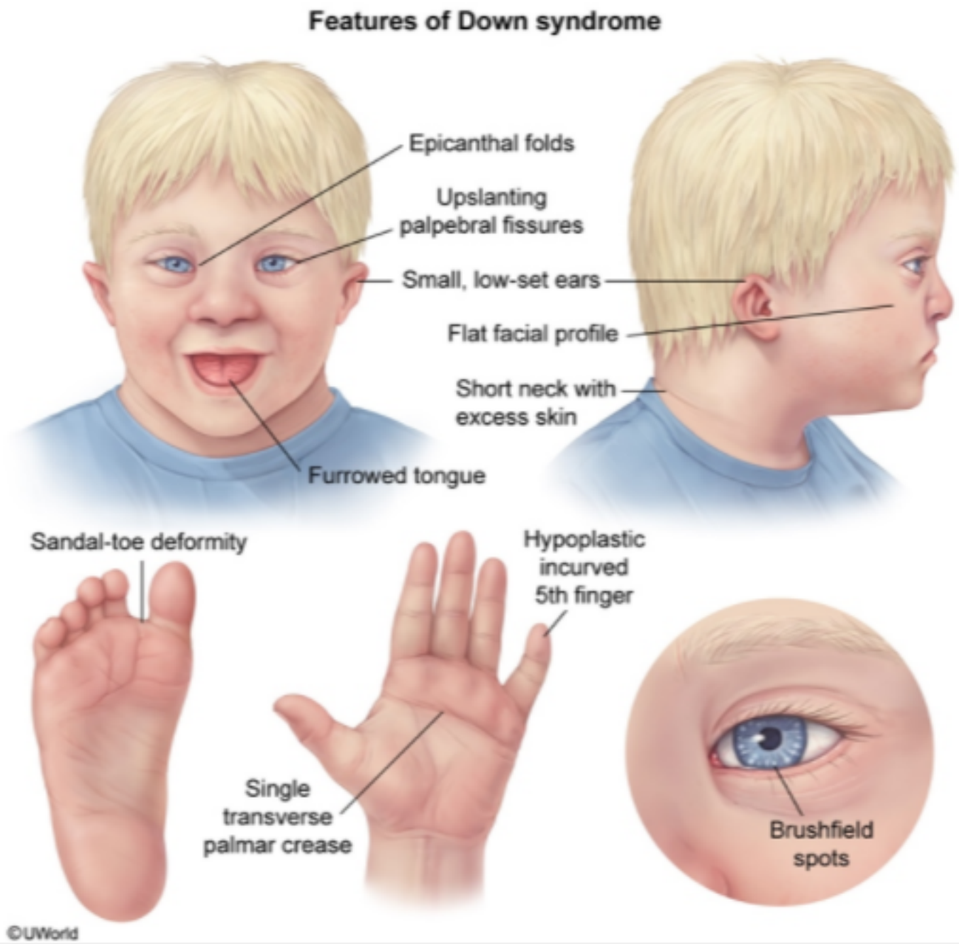

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References

- Maternal age and risk for trisomy 21 assessed by the origin of chromosome nondisjunction: a report from the Atlanta and National Down Syndrome Projects.
- Risk factors for nondisjunction of trisomy 21.

Genetics	Cardiovascular System	Down syndrome
Subject	System	Topic

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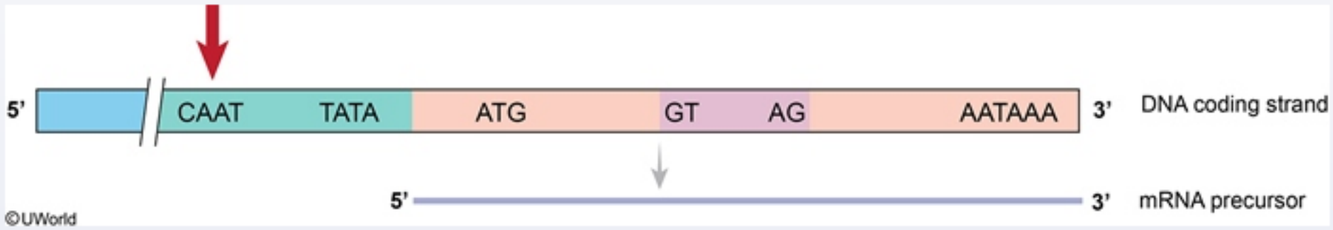
A 6-year-old girl with chronic anemia requiring repeated blood transfusions is undergoing genetic testing. The patient's mother and older sibling have a history of mild anemia. Her peripheral blood smear shows hypochromic, microcytic red blood cells, and hemoglobin electrophoresis reveals a predominance of hemoglobins F and A2. Sequencing of the β-globin gene is performed using the patient's erythroblast DNA. A schematic representation of the gene and its transcribed RNA is shown in the image below.



The base sequence indicated by the bold red arrow is responsible for which of the following functions?

- A. Enhancement of transcription
- B. Initiation of transcription
- C. Initiation of translation
- D. Repression of transcription
- E. Termination of transcription

Submit

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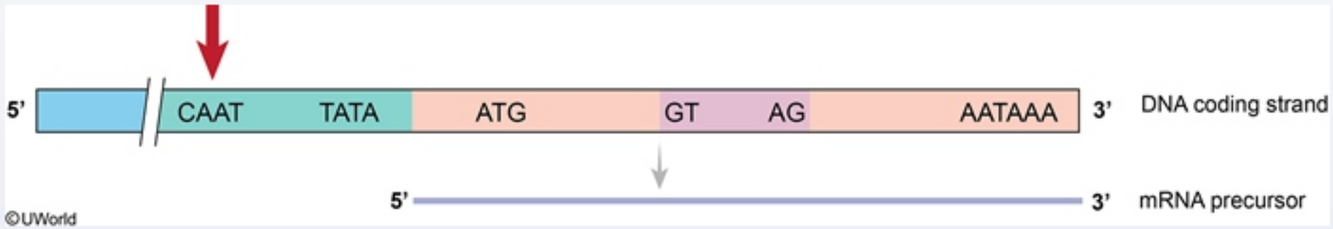

The base sequence indicated by the bold red arrow is responsible for which of the following functions?

- A. Enhancement of transcription (26%)
- ✓ B. Initiation of transcription (64%)
- C. Initiation of translation (4%)
- D. Repression of transcription (2%)
- E. Termination of transcription (2%)

Omitted
Correct answer
B

64%
Answered correctly

03 secs
Time Spent

02/21/2020
Last Updated

Explanation

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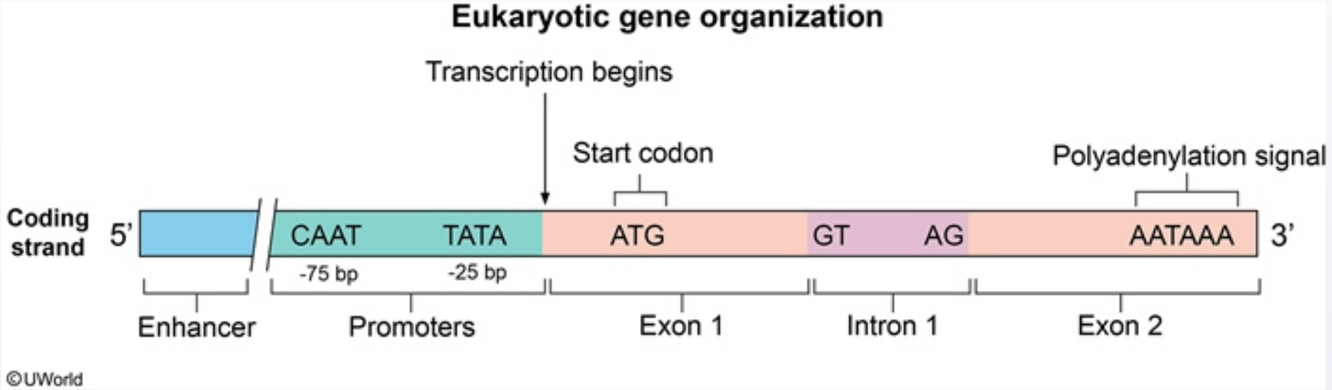

This patient with chronic microcytic anemia requiring blood transfusions and a predominance of hemoglobins F and A2 on hemoglobin electrophoresis likely has beta-thalassemia, a hereditary blood disorder characterized by reduced β-globin chain production.

The base sequence indicated by the bold red arrow in this patient's β-globin gene represents the **CAAT box**, a highly conserved (consensus) sequence that functions as a **promoter of transcription** in the **eukaryotic** genome. It is typically located 70-80 bases upstream from the transcription start site. The Hogness (TATA) box is a second promoter region in the eukaryotic genome and is seen just to the right of the CAAT box in the above image. The TATA box is generally located 25 bases upstream from the transcription start site. Both the CAAT box and the TATA box promote initiation of transcription by acting as binding sites for general **transcription factors and RNA polymerase II**.

(Choice A) Enhancer sequences bind activator proteins that facilitate bending of DNA. DNA bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the rate of transcription. Enhancers can be located upstream or downstream from the gene being transcribed and may be near the gene or thousands of base pairs away.

(Choice C) Translation is initiated in the cytoplasm when a ribosome recognizes the AUG (methionine) start codon on a mature mRNA strand. The Kozak consensus sequence plays a major role in initiation of the eukaryotic translation process.

(Choice D) Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

(Choice E) Eukaryotic transcription termination is not completely understood. In prokaryotes, a palindromic code in the DNA template causes formation of a "hairpin" turn in the newly synthesized mRNA, which facilitates detachment of RNA polymerase from the DNA template.

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Educational objective:
The TATA and CAAT boxes are promoters of transcription in eukaryotic cells and are located approximately 25 and 75 bases upstream from the transcription start site, respectively. They promote initiation of transcription by serving as binding sites for transcription factors and RNA polymerase II.

References

- RNA polymerase II transcription initiation: a structural view.

Genetics	General Principles	Transcription
Subject	System	Topic

This patient with chronic microcytic anemia requiring blood transfusions and a predominance of hemoglobins F and A2 on hemoglobin

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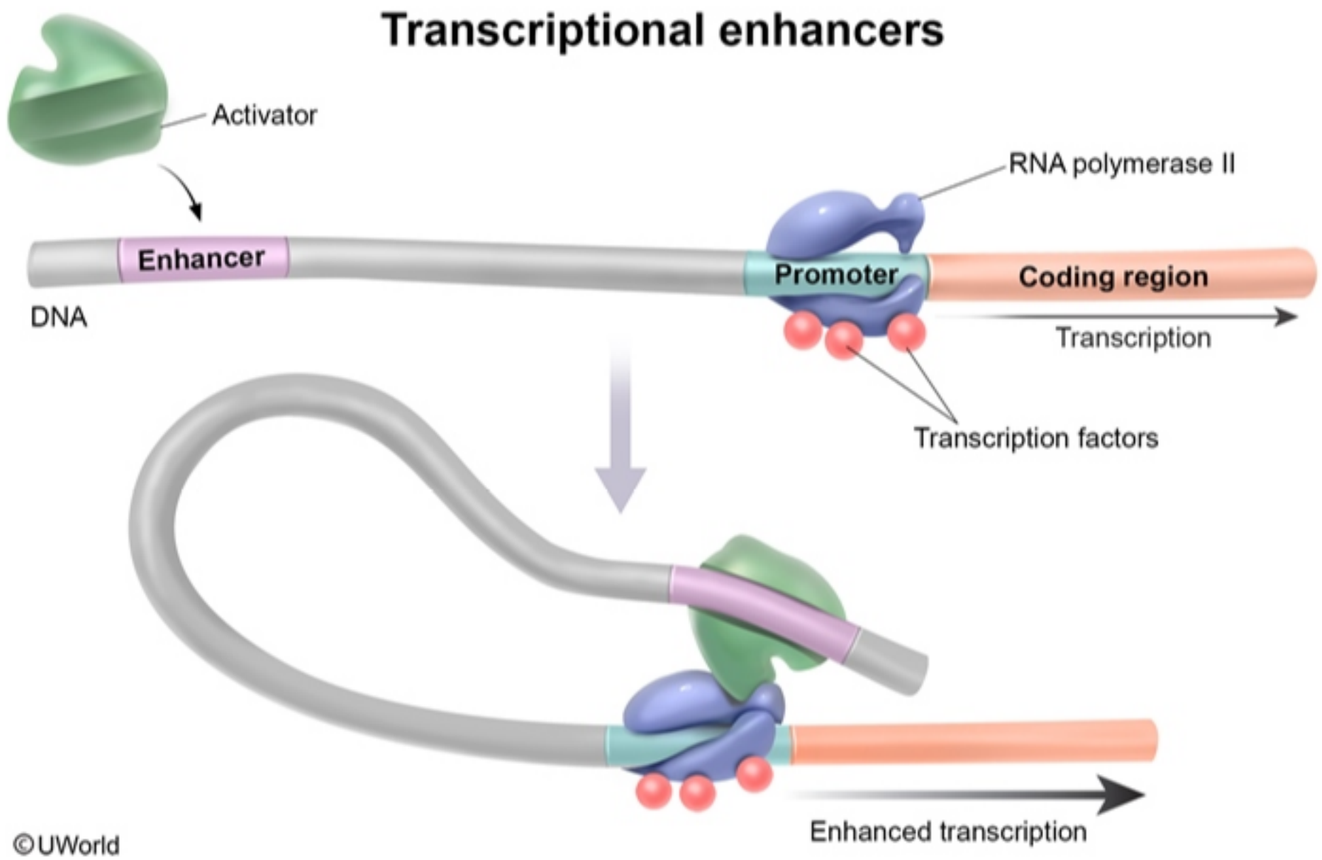

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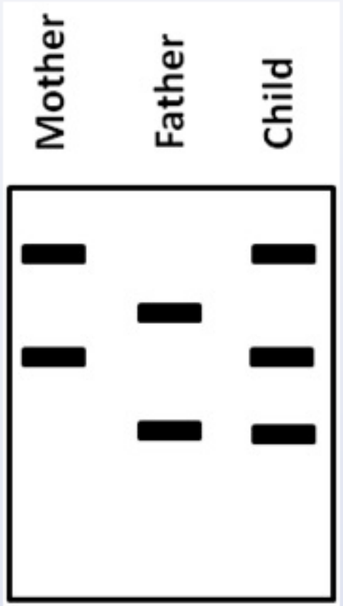
Subject System Topic

An infant born to a 34-year-old woman has a flat facial profile, prominent epicanthal folds, and a holosystolic murmur heard loudest at the left sternal border. Karyotype analysis is consistent with trisomy 21. Maternal and paternal karyotypes are normal. A restriction fragment length polymorphism (RFLP) analysis is conducted to determine the parental origin of the extra chromosome. DNA samples from the child, mother, and father are obtained and the DNA is fragmented with a restriction enzyme. The fragments are then sorted by size using the Southern blot technique. Labeling is done using a probe that binds to a specific DNA sequence close to the centromere of chromosome 21. RFLP analysis for the child, mother, and father is shown below.



In which of the following meiosis events did the nondisjunction most likely occur?

A. Maternal meiosis I

B. Maternal meiosis II

C. Paternal meiosis I

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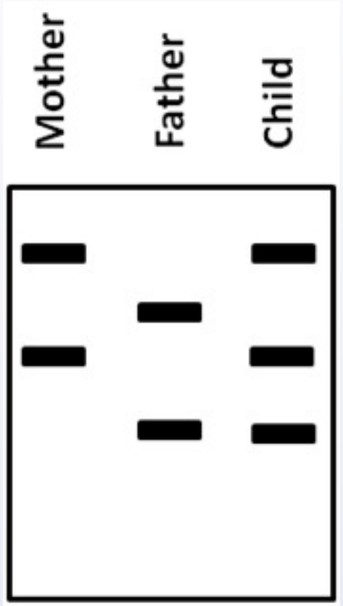
the child, mother, and father is shown below.

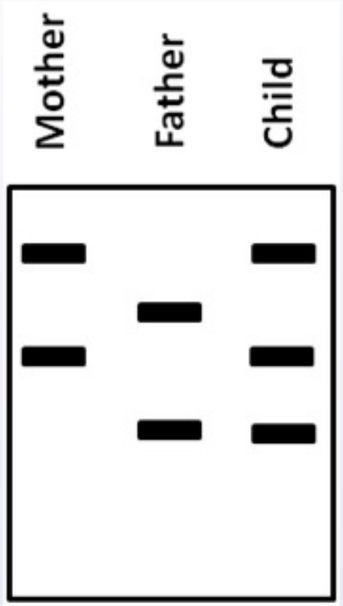


In which of the following meiosis events did the nondisjunction most likely occur?

- A. Maternal meiosis I
- B. Maternal meiosis II
- C. Paternal meiosis I
- D. Paternal meiosis II

Submit

the child, mother, and father is shown below.



In which of the following meiosis events did the nondisjunction most likely occur?

- A. Maternal meiosis I (52%)
- B. Maternal meiosis II (36%)
- C. Paternal meiosis I (5%)
- D. Paternal meiosis II (5%)

Omitted
Correct answer

52%
Answered correctly

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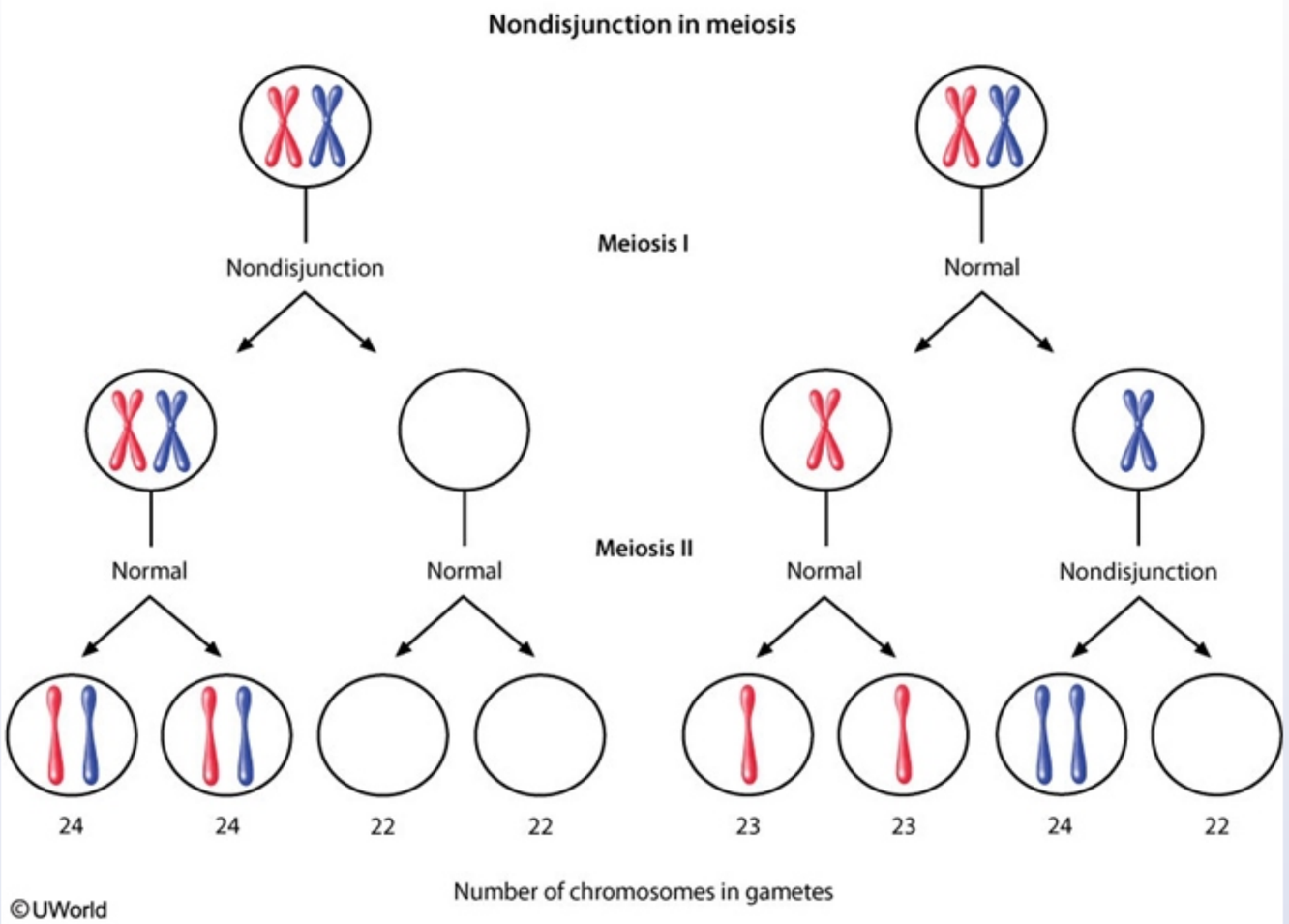
Last Updated



Nondisjunction is the **failure of chromosome pairs to separate** properly during cell division. This could be due to a failure of **homologous chromosomes** to separate in **meiosis I** or a failure of **sister chromatids** to separate during **meiosis II or mitosis**. In monosomy, a single chromosome is lost. In trisomy, a single chromosome is gained. **Monosomies or trisomies** can result from nondisjunction in meiosis I or II.

Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each parental band represents a

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Restriction fragment length polymorphism (RFLP) analysis shows that both parents demonstrate 2 bands. Each parental band represents a homologous chromosome 21. The child has 3 bands, indicating that he has 3 different versions of chromosome 21 that he obtained from his parents. He received the lower band from the father and both of the upper bands from the mother. The fact that he received 2 different bands from the mother indicates that he inherited both of her homologous chromosomes. Therefore, the problem occurred in the mother during meiosis I, when homologous chromosomes are separated. In fact, the vast majority of **Down syndrome** cases arise due to nondisjunction during maternal meiosis I.

(Choice B) If the mother had a failure in meiosis II, the child's RFLP analysis would reveal only two bands (see example). There would be a single band from the father and a darker, thicker band from the mother. The darker, thicker band signifies the inheritance of both sister chromatids, which will produce equal-size restriction fragments (but twice the normal amount).

(Choice C) If the father had a failure in meiosis I, the child's RFLP analysis would reveal 3 bands (see example). In this instance, there would be a single band inherited from the mother with two bands inherited from the father.

(Choice D) If the father had a failure in meiosis II, the child's RFLP analysis would reveal two bands (see example). In this instance, there would be a single band inherited from the mother and a second band from the father. The father's band would be darker and thicker, signifying the inheritance of both sister chromatids.

Educational objective:
Nondisjunction is the failure of chromosome pairs to separate properly during cell division. This could be due to a failure of homologous chromosomes to separate in meiosis I or a failure of sister chromatids to separate during meiosis II or mitosis.

References

- The meiotic stage of nondisjunction in trisomy 21: determination by using DNA polymorphisms.

Genetics General Principles Cell cycle

Nondisjunction is the **failure of chromosome pairs to separate** properly during cell division. This could be due to a failure of **homologous**

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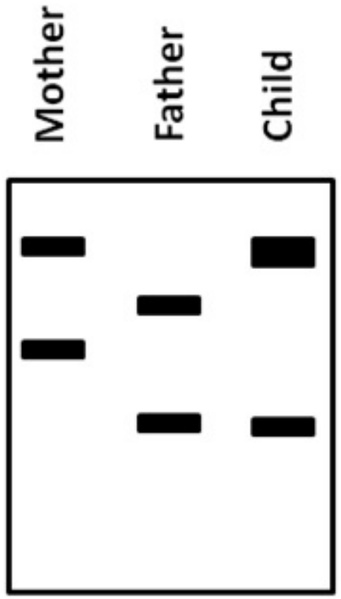

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Genetics General Principles Cell cycle

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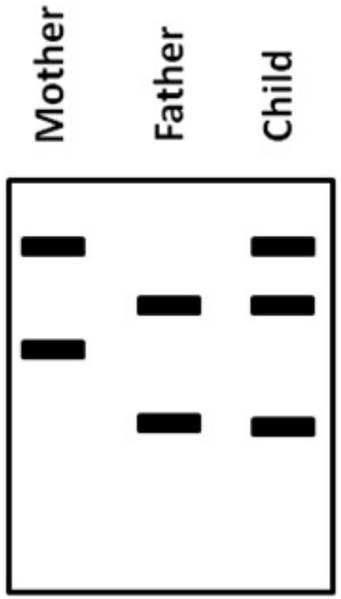

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Genetics | General Principles | Cell cycle

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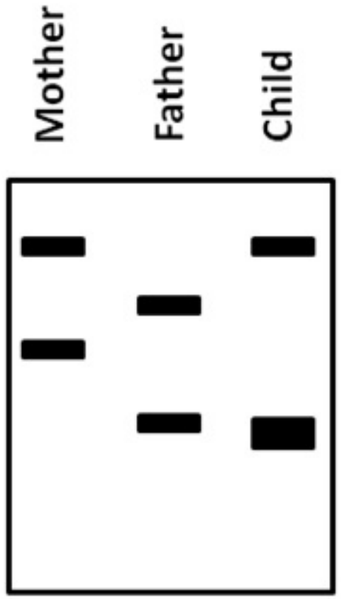

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Genetics | General Principles | Cell cycle

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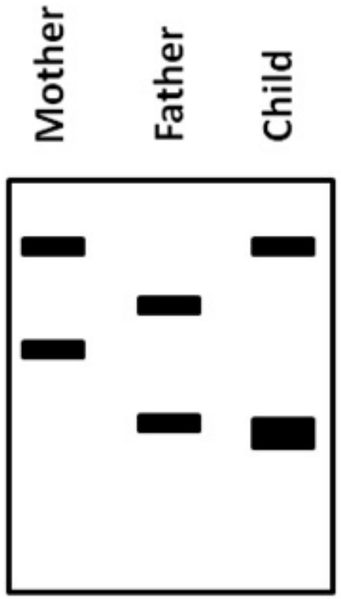

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Genetics | General Principles | Cell cycle

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A pharmaceutical researcher is evaluating a nuclear enzyme inhibitor for the treatment of an inherited disorder. During an experiment, he extracts and purifies nuclear enzymes from skin cells of an affected patient. One of these enzymes is found to catalyze the methylation of cytosine residues in DNA using S-adenosyl-methionine (SAM) as the methyl donor. This enzyme most likely plays a crucial role in which of the following genetic processes?

A. Aneuploidy
B. Epistasis
C. Imprinting
D. Meiotic nondisjunction
E. Pleiotropy

Submit

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- A. Aneuploidy (4%)
- B. Epistasis (7%)
- ✓ C. Imprinting (73%)
- D. Meiotic nondisjunction (5%)
- E. Pleiotropy (8%)

Omitted
Correct answer
C

73%
Answered correctly

02 secs
Time Spent

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Last Updated

Explanation

DNA methylation refers to the addition of methyl groups to nucleotide residues (often adenine and cytosine) by **DNA methyltransferase**, an enzyme that uses S-adenosyl-methionine (SAM) as the methyl group donor.

DNA methylation is an epigenetic process by which eukaryotic organisms modify gene expression without altering the genetic code. For example, methylation of cytosine-guanine dinucleotide repeats (CpGs) in the promoter region of genes effectively silences transcription of those genes. Fragile X syndrome is an X-linked disorder caused by an increased number of CGG trinucleotide repeats on the fragile X mental retardation 1

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Cytosine methylation is also used in **genomic imprinting**, a phenomenon in which an offspring's genes are expressed in a parent-specific manner. For instance, an allele inherited from the father may be inactivated or "imprinted" by methylation so that only the allele from the mother is expressed.

(Choices A and D) Aneuploidy refers to the presence of an abnormal number of chromosomes and is the result of chromosomal nondisjunction during mitosis or meiosis.

(Choice B) Epistasis is a phenomenon in which the allele of one gene affects the phenotypic expression of alleles in another gene.

(Choice E) Pleiotropy refers to the phenomenon in which a single gene influences multiple phenotypic traits.

Educational objective:
Genomic imprinting refers to the phenomenon in which an offspring's genes are expressed in a parent-specific manner. Genomic imprinting is caused by DNA methylation, an epigenetic process in which genes can be silenced by attaching methyl groups to cytosine residues in the DNA molecule.

References

- Mammalian Genomic Imprinting.

Genetics	General Principles	Transcription
Subject	System	Topic

DNA methylation refers to the addition of methyl groups to nucleotide residues (often adenine and cytosine) by **DNA methyltransferase**, an enzyme that uses S-adenosyl-methionine (SAM) as the methyl group donor.

DNA methylation is an epigenetic process by which eukaryotic organisms modify gene expression without altering the genetic code. For example, methylation of cytosine-guanine dinucleotide repeats (CpGs) in the promoter region of genes effectively silences transcription of those genes. Fragile X syndrome is an X-linked disorder caused by an increased number of CGG trinucleotide repeats on the fragile X mental retardation 1 (*FMR1*) gene, leading to hypermethylation of cytosine residues and *FMR1* inactivation.

Cytosine methylation is also used in **genomic imprinting**, a phenomenon in which an offspring's genes are expressed in a parent-specific manner. For instance, an allele inherited from the father may be inactivated or "imprinted" by methylation so that only the allele from the mother is expressed.

(Choices A and D) Aneuploidy refers to the presence of an abnormal number of chromosomes and is the result of chromosomal nondisjunction during mitosis or meiosis.

(Choice B) Epistasis is a phenomenon in which the allele of one gene affects the phenotypic expression of alleles in another gene.

(Choice E) Pleiotropy refers to the phenomenon in which a single gene influences multiple phenotypic traits.

Educational objective:
Genomic imprinting refers to the phenomenon in which an offspring's genes are expressed in a parent-specific manner. Genomic imprinting is caused by DNA methylation, an epigenetic process in which genes can be silenced by attaching methyl groups to cytosine residues in the DNA molecule.

References

- Mammalian Genomic Imprinting.

Genetics	General Principles	Transcription
Subject	System	Topic

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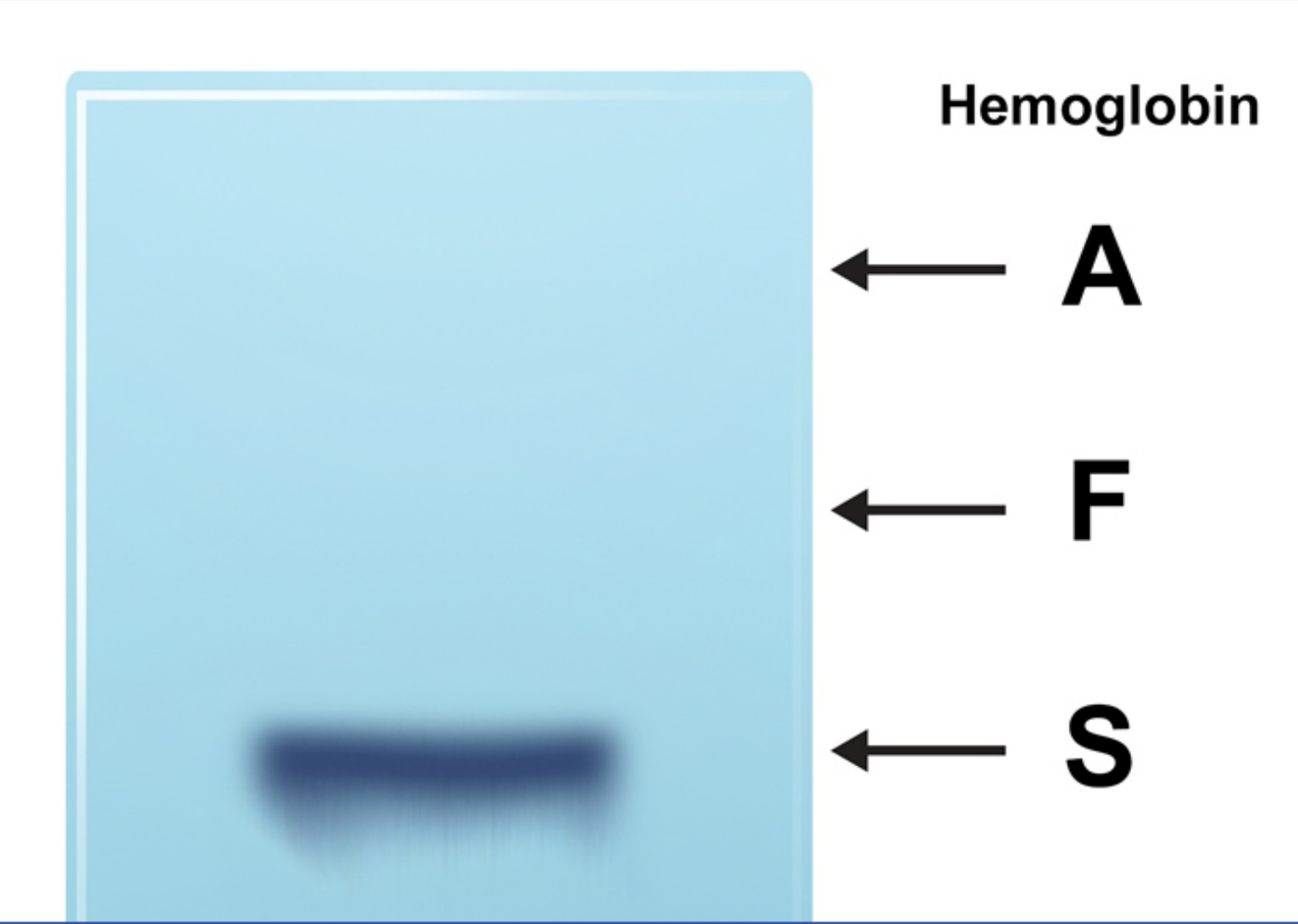
A 26-year-old woman comes to the office with her husband for genetic counseling. She is pregnant with their second child, whose gender is unknown. Both parents are asymptomatic, but their firstborn 3-year-old son has recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. A blood sample is obtained from the boy, and hemoglobin electrophoresis is performed at alkaline pH. The results are shown in the image below.



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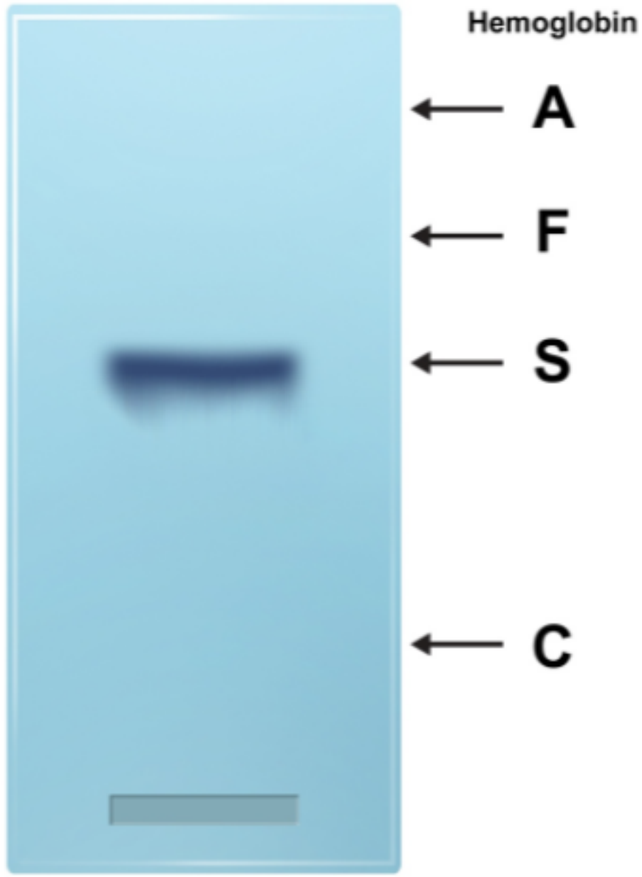

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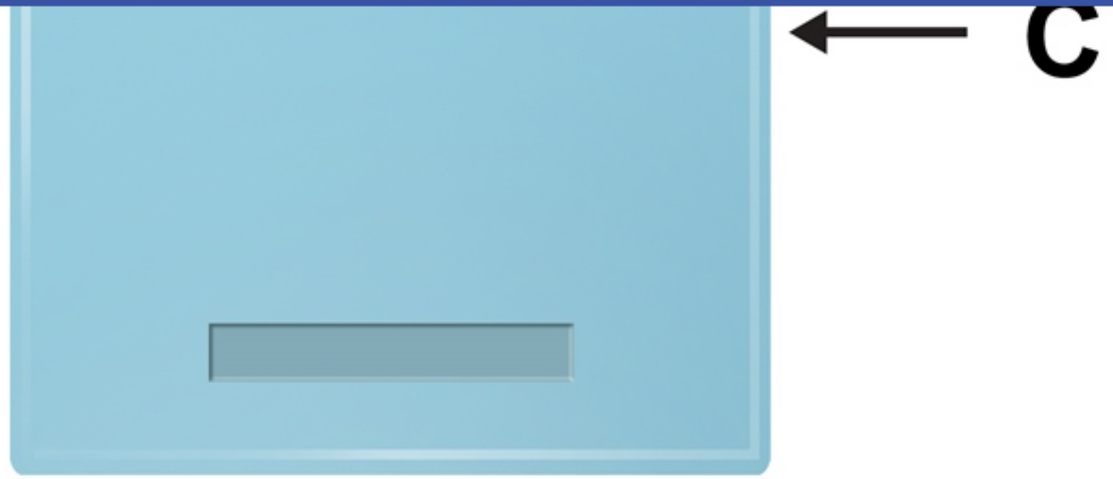

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What is the probability that the unborn child will inherit one or more mutant alleles from the parents?

- A. Near 0
- B. 25%
- C. 50%
- D. 75%
- E. 100%

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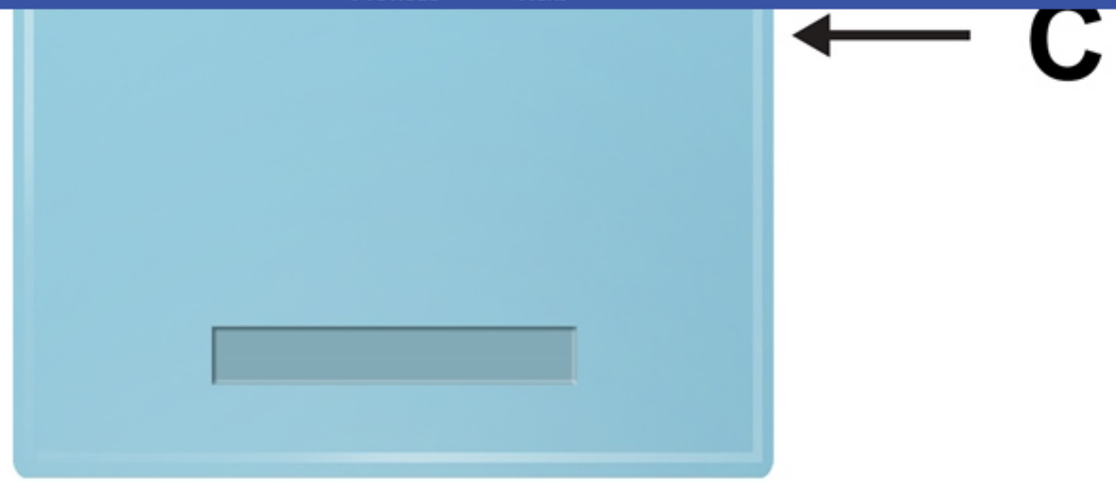

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What is the probability that the unborn child will inherit one or more mutant alleles from the parents?

- A. Near 0 (0%)
- B. 25% (17%)
- C. 50% (7%)
- ✓ D. 75% (69%)
- E. 100% (4%)

Omitted
Correct answer

69%
Answered correctly

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Autosomal recessive inheritance

Carrier parent (Aa)	A	a
A	AA Normal child	Aa Carrier child
a	Aa Carrier child	aa Affected child

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Exhibit Display

Autosomal recessive inheritance

Carrier parent (Aa)

Carrier parent (Aa)	A	a
A	AA Normal child	Aa Carrier child
a	Aa Carrier child	aa Affected child

Offspring have 75% chance of inheriting at least 1 mutant allele

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The couple's 3-year-old son has **sickle cell anemia**, an **autosomal recessive** disorder that causes red blood cells to assume a sickle shape during times of hypoxic stress, resulting in painful and potentially life-threatening vasoocclusive crises. The disease can be diagnosed using hemoglobin electrophoresis, which is able to determine the different types of hemoglobin in a blood sample based on their electrical charge and the speed by which they move through the medium. The patient's electrophoresis results show a predominance of hemoglobin S (HbS), which is diagnostic for sickle cell disease.

In this case, both **parents are unaffected** and must be **heterozygous carriers** (Aa) of the disorder because they have an **affected child**. This means that each parent has a 50% chance of passing either a normal allele (A) or a mutant allele (a) to the offspring. The possible genotypes of the unborn child can be calculated using a Punnett square and are as follows:

- 25% chance of inheriting two normal alleles (AA, child is unaffected)
- 50% chance of inheriting one normal and one mutant allele (Aa or aA, child is a carrier)
- 25% chance of inheriting two mutant alleles (aa, child is affected)

Only the last 2 options result in the child inheriting a mutant allele, so the probability that the unborn child is carrying **one or more mutant alleles** is 75%.

(Choice B) The probability of the unborn child being affected is equivalent to the chance of inheriting two mutant alleles from the carrier parents, which is 25%. However, this question asks for the probability that the unborn child will inherit one or more mutant alleles (ie, chance of having the disease or being a carrier).

Educational objective:
Sickle cell anemia is an autosomal recessive disease that results in recurrent episodes of anemia, jaundice, and painful swelling of the hands and feet. Offspring of carrier parents have a 25% chance of being affected and a 50% chance of being heterozygous carriers, resulting in a 75% chance of inheriting at least one mutant allele.

References

- Hematologic Disorders: Sickle Cell Disease.

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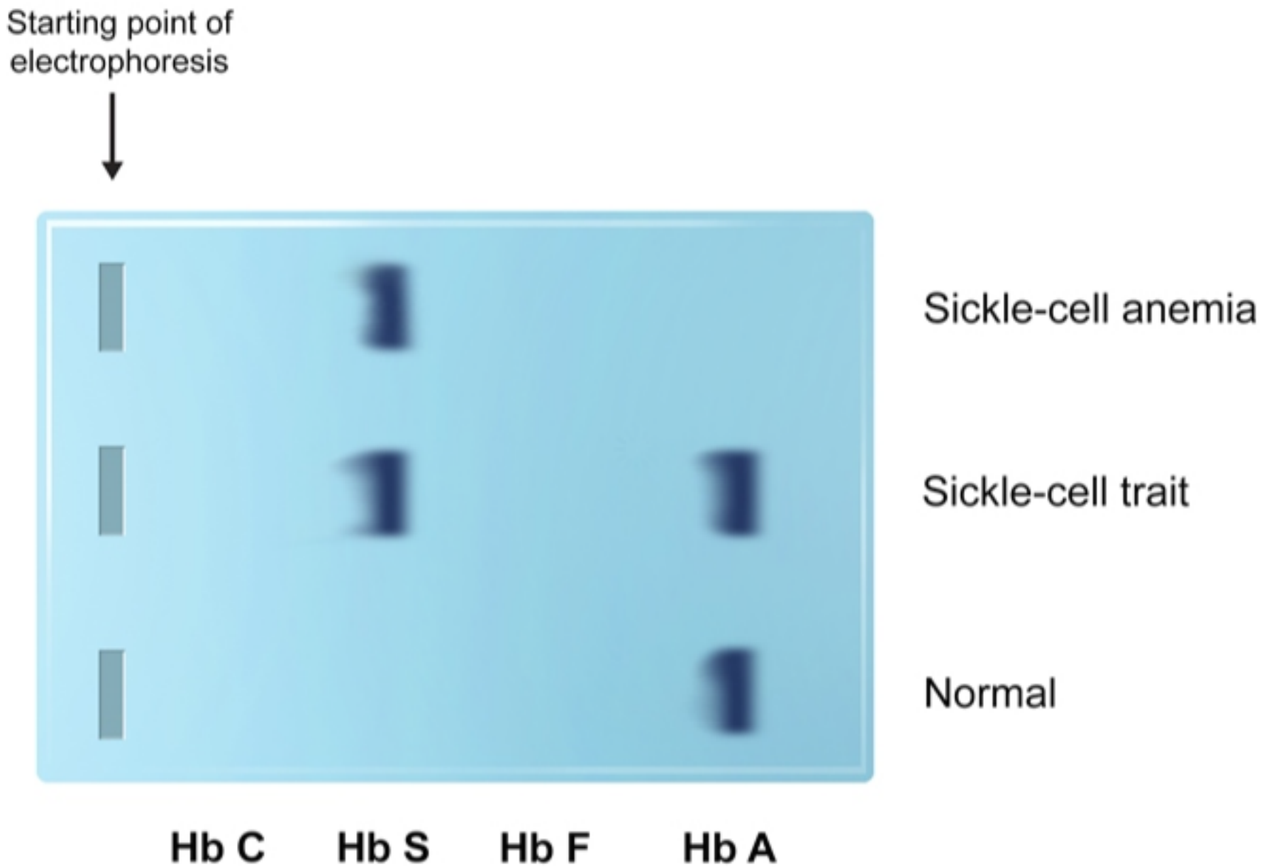

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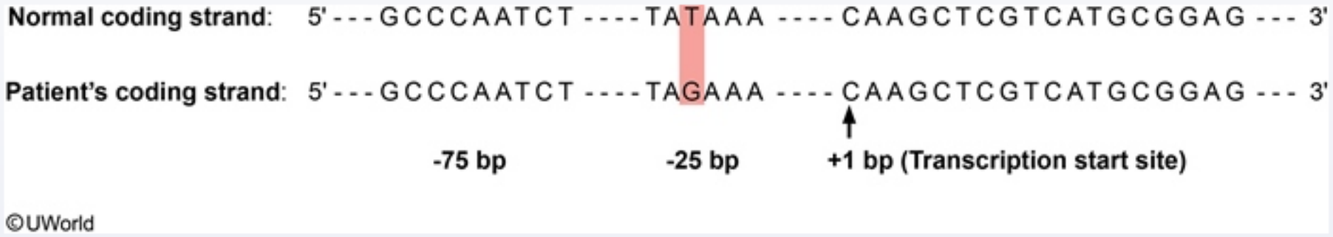
A genetic study performed on a 10-year-old boy reveals a single base substitution mutation involving a DNA segment that encodes a cellular protein, as shown in the image below.



This mutation is most likely to affect which of the following processes?

- A. DNA methylation
- B. Polypeptide folding following translation
- C. Posttranscriptional RNA splicing
- D. RNA elongation
- E. Transcription initiation
- F. Translation initiation

Submit

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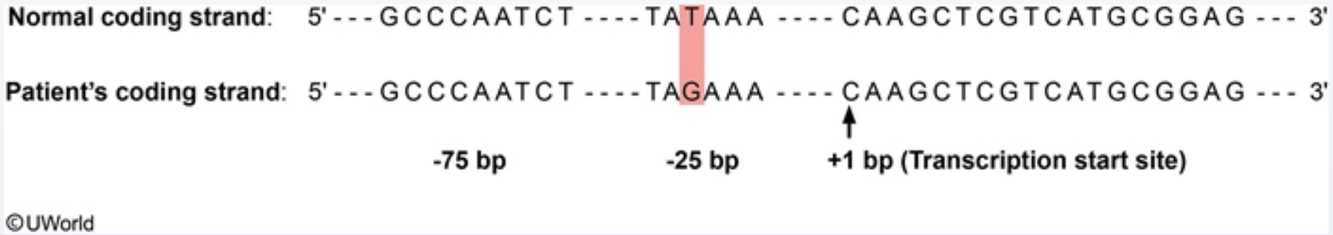

This mutation is most likely to affect which of the following processes?

- A. DNA methylation (2%)
- B. Polypeptide folding following translation (3%)
- C. Posttranscriptional RNA splicing (4%)
- D. RNA elongation (2%)
- ✓ E. Transcription initiation (82%)
- F. Translation initiation (4%)

Omitted
Correct answer
E

82%
Answered correctly

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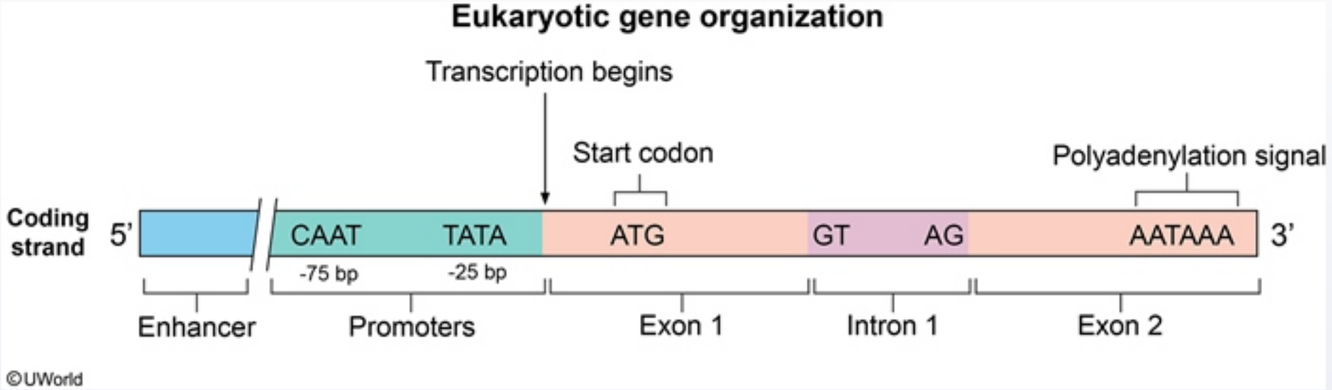
Explanation



Genetic information flows from DNA to RNA to proteins. Most eukaryotic DNA sequences consist of coding exons, noncoding introns, and 2 **promoter regions** (the CAAT box and the TATA box). The CAAT box is located 70-80 bases upstream of the beginning (5' end) of the coding region, and the **TATA box** is located **25 bases upstream** from the beginning of the coding region.

Gene transcription begins when **RNA polymerase II** attaches to one of the promoter regions in a process that requires general **transcription factors**. A DNA enhancer region then binds activator proteins that associate with transcription factors and RNA polymerase II at the promoter, thereby increasing gene expression. Although promoters are not directly translated into protein, promoter mutations can cause abnormal gene expression by altering the ability of RNA polymerase II and transcription factors to bind.

(Choice A) DNA methylation is part of the epigenetic code. This process is carried out by DNA methyltransferases and serves to silence the genes it affects.

(Choice B) The folding of a formed polypeptide into its secondary and tertiary structures is entirely spontaneous and is determined by the amino acid sequence in the protein's primary structure. Heat shock proteins assist in the spontaneous refolding of proteins.

(Choice C) Posttranscriptional RNA splicing is facilitated by small nuclear ribonucleoproteins (snRNPs) that remove introns from heterogeneous nuclear RNA (hnRNA) containing GU at the 5' splice site and AG at the 3' splice site.

(Choice D) The TATA box only participates in the initiation of transcription. The addition of nucleotides to the forming RNA molecule (RNA elongation) continues until RNA polymerase II encounters a termination signal.

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(Choice F) In eukaryotes, translation initiation requires both ribosomal subunits (60S and 40S) with their associated rRNA, mRNA, initiation factors, initiator tRNA charged with methionine, and GTP. The assembled ribosome then recognizes the AUG start codon on mRNA to begin the process.

Educational objective:
The TATA box is a promoter region that binds transcription factors and RNA polymerase II during the initiation of transcription. It is located approximately 25 bases upstream from the beginning of the coding region.

References

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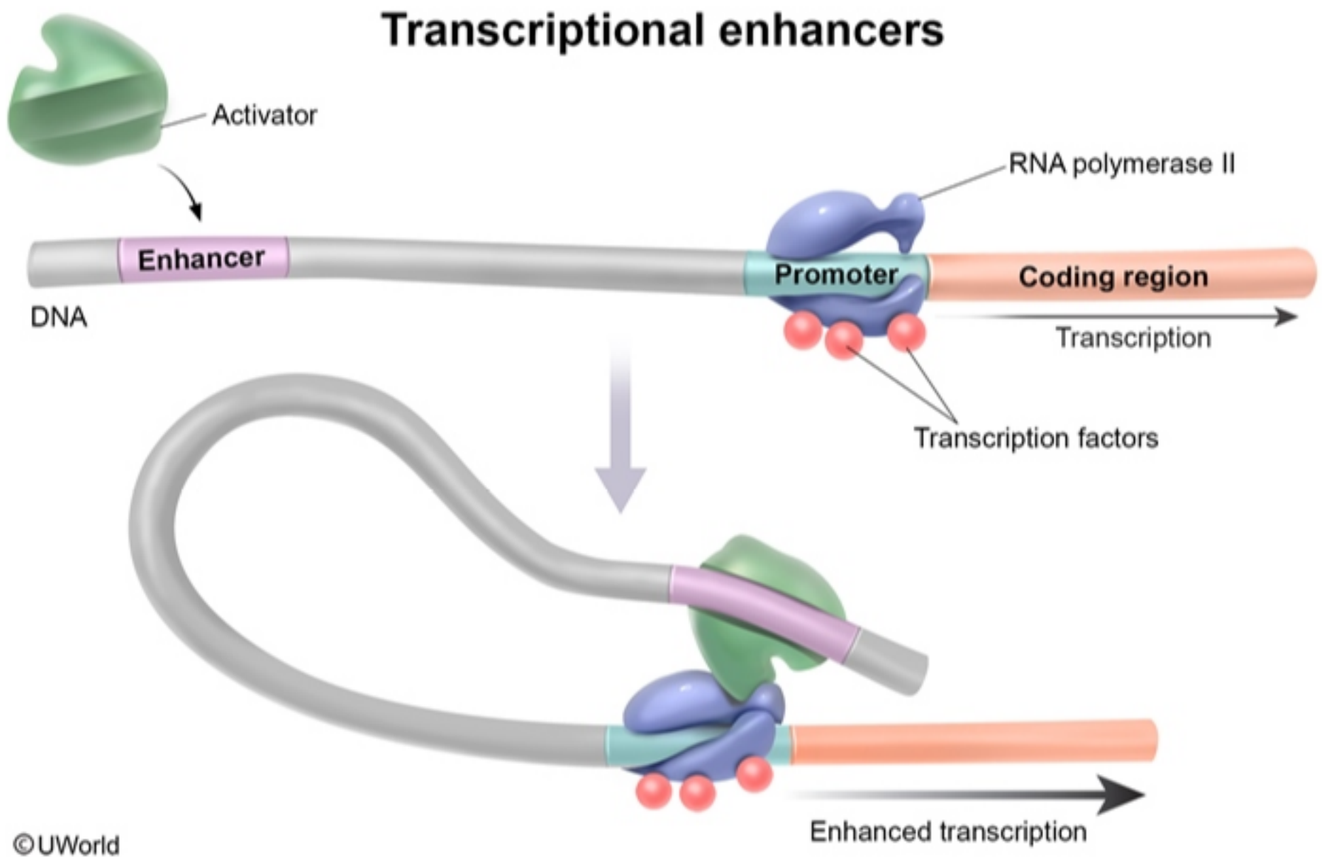

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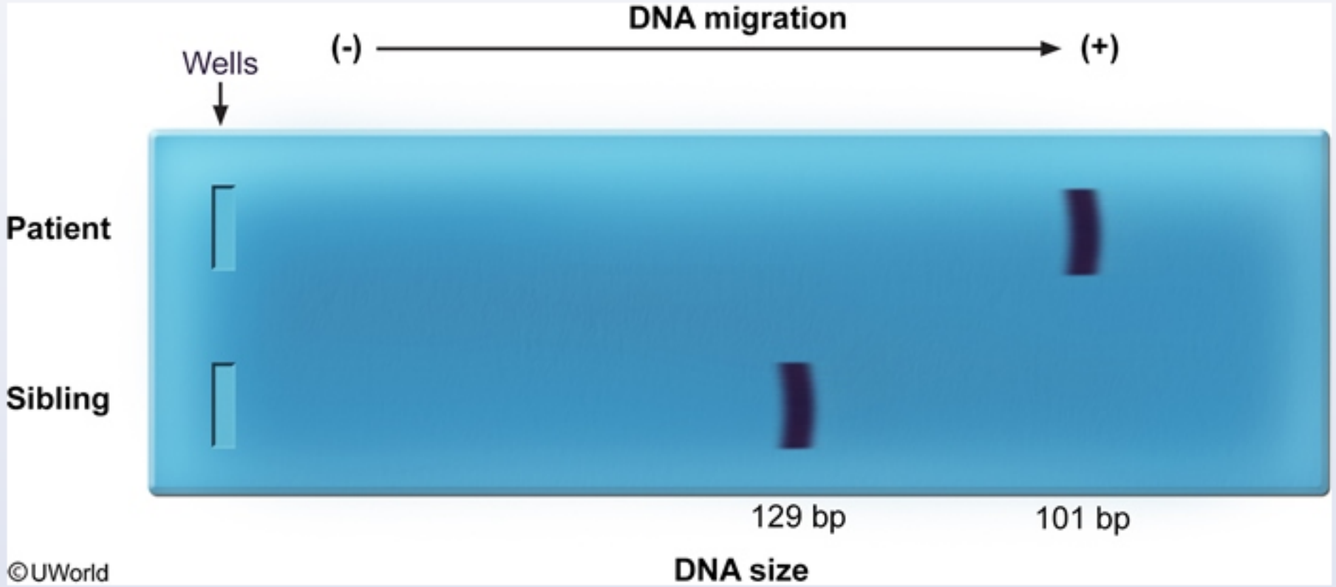
A 3-year-old boy is being evaluated for recurrent respiratory infections. The patient's family immigrated to the United States 5 months after his birth. Since then, the boy has experienced multiple episodes of pneumonia and bronchitis, and has developed a persistent cough and failure to thrive. His older brother has no medical issues. A genetic test is performed and reveals a mutation in an exon of a gene that codes for a transmembrane chloride channel. The abnormal mRNA is isolated from cultured epithelial cells, and its complementary DNA is synthesized. Amplified cDNA samples from both the patient and his healthy sibling are analyzed using gel electrophoresis and compared to DNA fragments of known size to determine base pair length. The results are shown below.



Which of the following is most likely responsible for this patient's condition?

A. Frameshift mutation
B. In-frame deletion
C. Missense mutation

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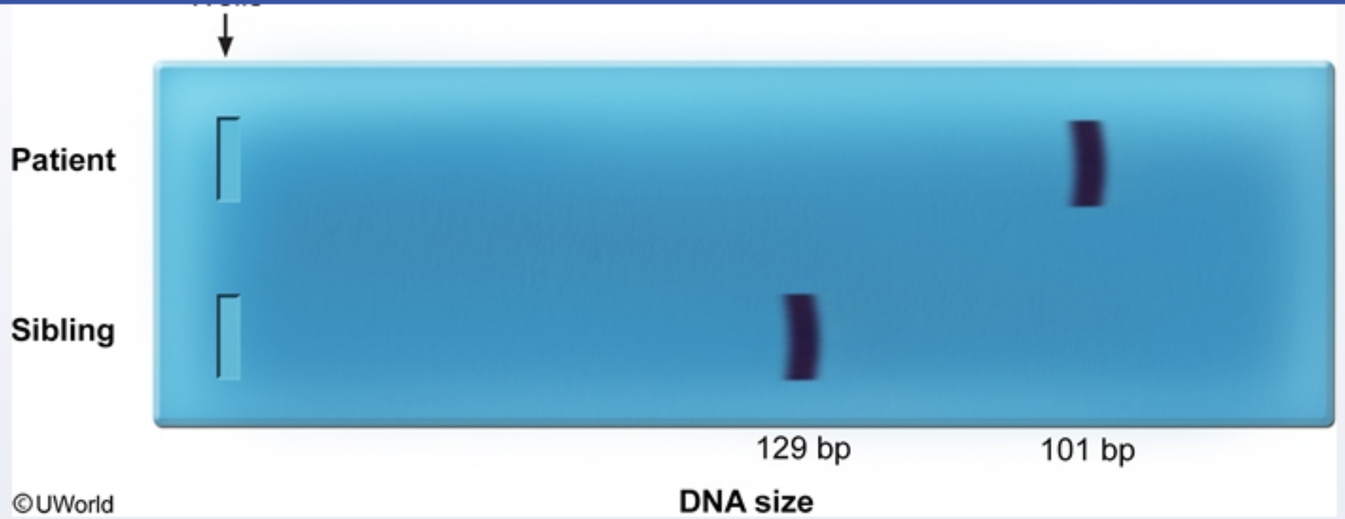

Which of the following is most likely responsible for this patient's condition?

- A. Frameshift mutation
- B. In-frame deletion
- C. Missense mutation
- D. Nonsense mutation
- E. Silent mutation
- F. Trinucleotide expansion

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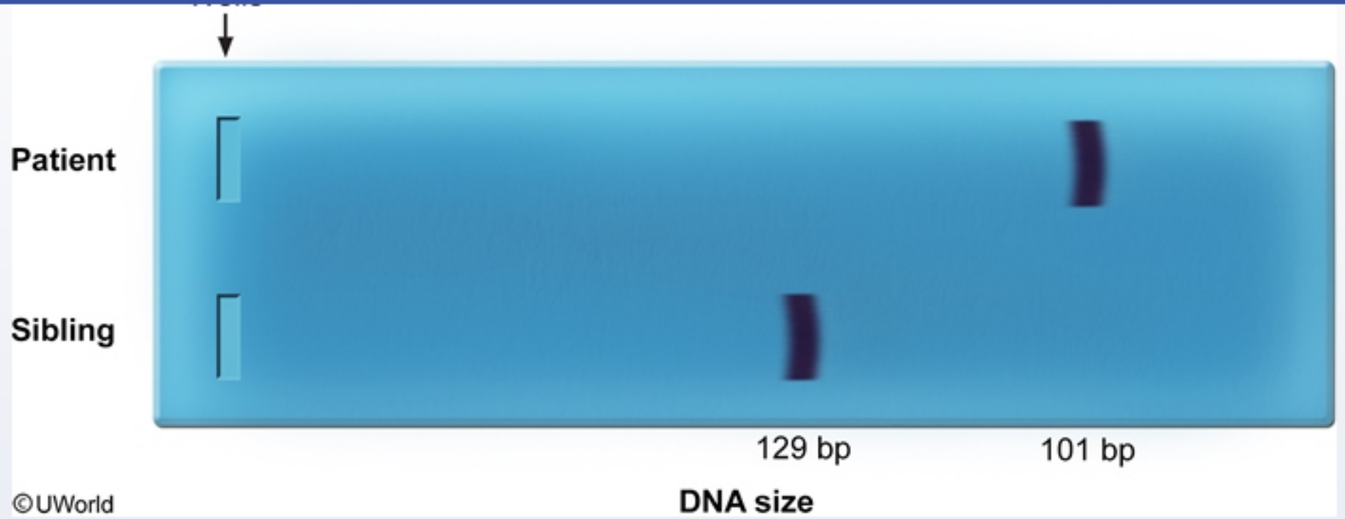

Which of the following is most likely responsible for this patient's condition?

- ✓ A. Frameshift mutation (24%)
- B. In-frame deletion (15%)
- C. Missense mutation (10%)
- D. Nonsense mutation (47%)
- E. Silent mutation (0%)
- F. Trinucleotide expansion (1%)

Omitted
Correct answer

24%
Answered correctly

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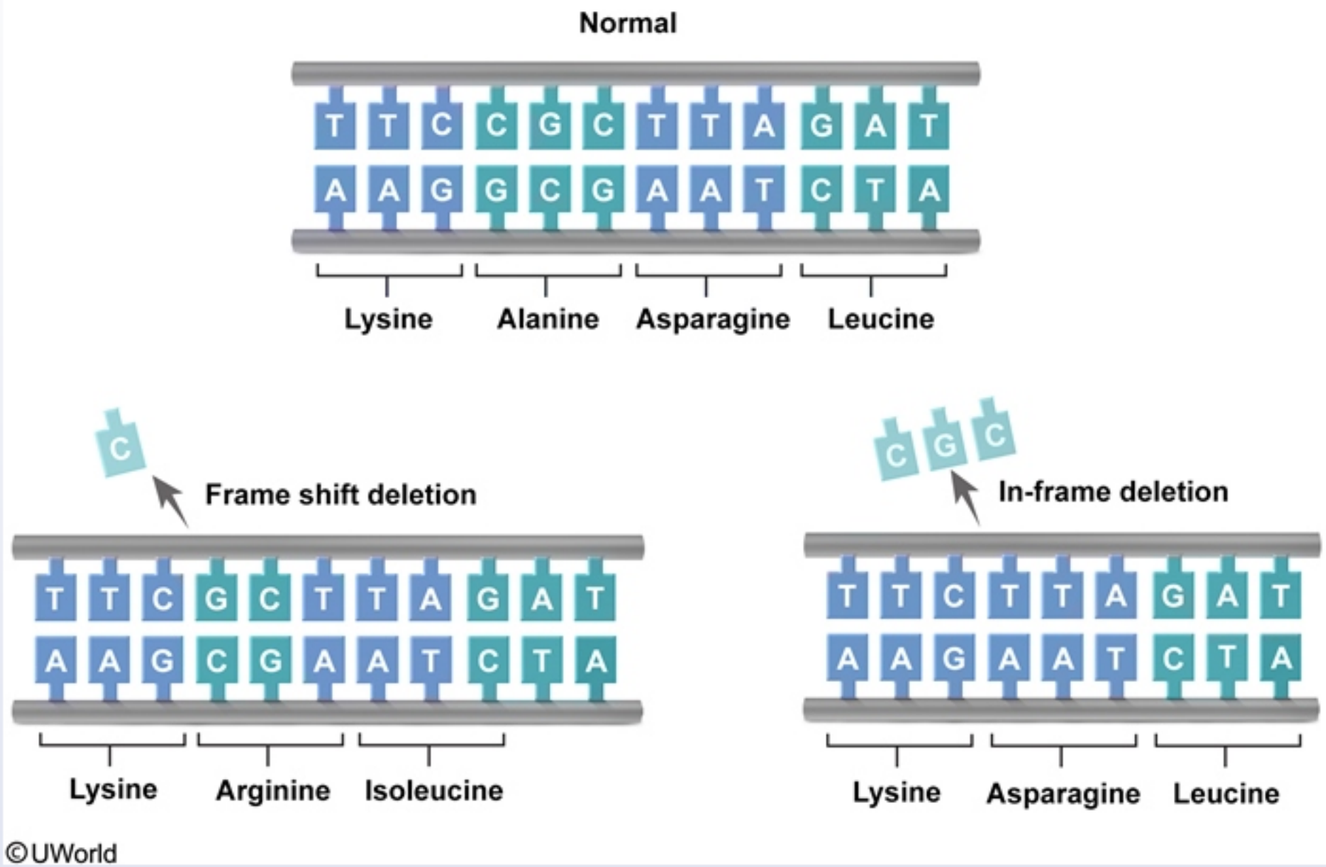

This patient has cystic fibrosis, which occurs due to mutations affecting the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The vignette states that the patient's **mutation affects an exon**, meaning that the mutation will be **detectable in the mRNA** sequence. Complementary DNA (cDNA) is double-stranded DNA that is synthesized from an mRNA template. In this case, cDNA was synthesized using *CFTR* mRNA from the patient and his brother. Subsequent gel electrophoresis shows that the patient's cDNA is 28 base pairs shorter than that of his brother, indicating the patient has a **28-base pair deletion** affecting the coding region of *CFTR*. Deletion or insertion of a number of bases that is **not divisible by 3** results in **frameshift mutations**. As the name implies, frameshift mutations alter the reading frame of the genetic code,

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(Choice B) One or more complete codons (genetic triplet codes) are removed in an in-frame deletion, which does not affect the reading frame of subsequent codons. This patient's 28-base pair deletion is not divisible by 3, so it will result in a reading frame shift.

(Choices C and D) Missense and nonsense mutations are due to single base substitutions that result in the placement of an incorrect amino acid or introduction of a premature stop codon, respectively. These mutations occur in exons and affect protein translation. However, in this scenario, **gel electrophoresis** is being performed on **cDNA (not protein)** and the results indicate the **length of the mature RNA transcript**. Termination of RNA transcription occurs by specific sequences in the 3' untranslated region that cause RNA hairpin loop formation and/or recruitment of termination factors. As a result, point mutations in the exons of a gene (such as those responsible for causing nonsense mutations) are unlikely to affect total mRNA (cDNA) size.

(Choice E) Silent mutations can occur in both coding and noncoding regions, but they do not alter protein quantity or function and do not affect phenotype. This patient's mutation caused him to develop cystic fibrosis, so it is not a silent mutation.

(Choice F) Trinucleotide expansions increase the number of trinucleotide repeats in the coding region of a gene, often resulting in large proteins with abnormal function. This patient's abnormal *CFTR* gene is shorter (not longer) than the normal gene from his sibling, which indicates a deletion has occurred.

Educational objective:
Deletion or addition of a number of bases that is not divisible by 3 in the coding region of a gene will cause a frameshift mutation. Frameshift mutations alter the reading frame of the genetic code, resulting in the formation of nonfunctional proteins.

References

- The CFTR frameshift mutation 3905insT and its effect at transcript and protein level

resulting in the formation of nonfunctional proteins due to the incorporation of many incorrect amino acids.

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Genetics	General Principles	Mutations
Subject	System	Topic

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A cell biologist is studying the role of ribonucleoproteins in normal cellular function. He prepares a cell extract using a specific cell type obtained from a 73-year-old man. Ribonucleoproteins are separated and purified from the cell extract for structural and functional analyses. These cells are found to express higher amounts of a particular protein in comparison to other cell types. This protein has reverse transcriptase activity that functions to add TTAGGG repeats to the 3' end of chromosomes. Which of the following cell types was most likely studied in this experiment?

A. Epidermal basal cells
B. Erythrocytes
C. Myocardial cells
D. Neurons
E. Pancreatic β cells

Submit

A cell biologist is studying the role of ribonucleoproteins in normal cellular function. He prepares a cell extract using a specific cell type obtained from a 73-year-old man. Ribonucleoproteins are separated and purified from the cell extract for structural and functional analyses. These cells are found to express higher amounts of a particular protein in comparison to other cell types. This protein has reverse transcriptase activity that functions to add TTAGGG repeats to the 3' end of chromosomes. Which of the following cell types was most likely studied in this experiment?

- ✓ A. Epidermal basal cells (75%)
- B. Erythrocytes (3%)
- C. Myocardial cells (2%)
- D. Neurons (10%)
- E. Pancreatic β cells (7%)

Omitted
Correct answer
A

75%
Answered correctly

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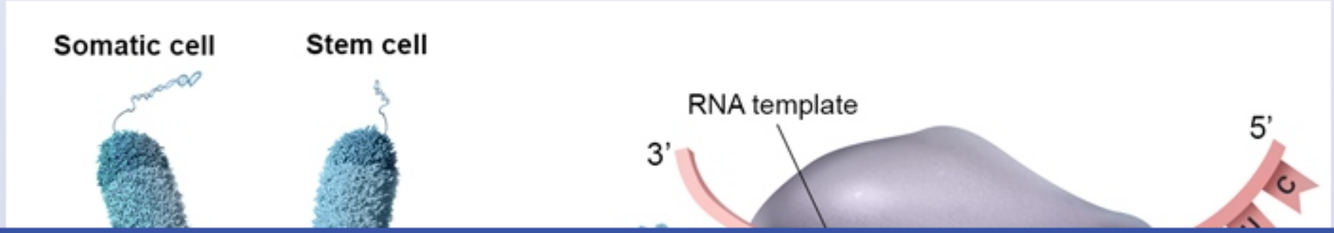

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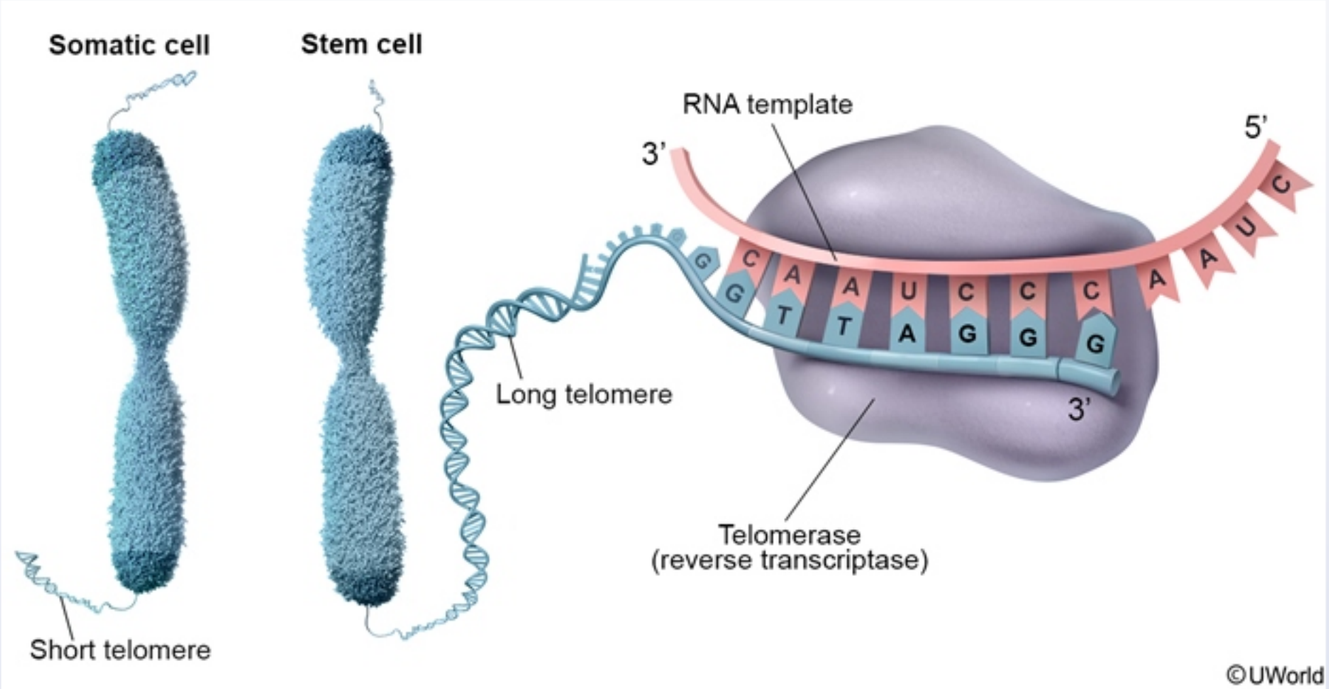

Telomerase is a ribonucleoprotein that adds **TTAGGG** repeats to the **3' end of chromosomes** (telomere region). It is similar to other reverse transcriptase enzymes in that it synthesizes single-stranded DNA using single-stranded RNA as a template (**RNA-dependent DNA polymerase**). Telomerase is composed of 2 main subunits, the telomerase reverse transcriptase (TERT) subunit and the telomerase RNA component (TERC). TERC is a "built-in" RNA template that is repeatedly read by the TERT subunit to add TTAGGG DNA sequence repeats to telomeres.

Stem cells have very **long telomeres** due to their high telomerase activity, allowing them to proliferate indefinitely in a controlled manner. In contrast, most terminally differentiated adult somatic cells (eg, myocardial cells, neurons, pancreatic β cells) have short telomeres as they do not

Short telomere

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Telomerase is a ribonucleoprotein that adds **TTAGGG** repeats to the **3' end of chromosomes** (telomere region). It is similar to other reverse transcriptase enzymes in that it synthesizes single-stranded DNA using single-stranded RNA as a template (**RNA-dependent DNA polymerase**). Telomerase is composed of 2 main subunits, the telomerase reverse transcriptase (TERT) subunit and the telomerase RNA component (TERC). TERC is a "built-in" RNA template that is repeatedly read by the TERT subunit to add TTAGGG DNA sequence repeats to telomeres.

Stem cells have very **long telomeres** due to their high telomerase activity, allowing them to proliferate indefinitely in a controlled manner. In contrast, most terminally differentiated adult somatic cells (eg, myocardial cells, neurons, pancreatic β cells) have short telomeres as they do not express telomerase and their telomeres shorten with every cell division **(Choices C, D, and E)**. Critical shortening in telomere length is thought to be a signal for programmed cell death. In fact, syndromes of premature aging (eg, Bloom syndrome) are associated with shortened telomeres. In contrast, cancer cells upregulate their telomerase activity, preventing cell death by maintaining their telomere length.

Stem cells are undifferentiated cells with the potential to differentiate into other cell types and can be classified as either embryonic or adult stem cells. Although embryonic stem cells are present in the very early stages of embryogenesis and can give rise to every cell type in adult humans (pluripotent), adult stem cells are present in most tissues and are generally responsible for replacing dead cells. For example, the epidermis is continuously replaced by stem cells present in the basal cell layers. Bone marrow stem cells similarly replace peripheral red and white blood cells.

(Choice B) Erythrocytes have no nuclei and therefore have no potential to divide.

Educational objective:
Critical shortening in telomere length can signal for programmed cell death. Telomerase is a reverse transcriptase (RNA-dependent DNA polymerase) that lengthens telomeres by adding TTAGGG repeats to the 3' end of chromosomes. Stem cells have long telomeres due to high telomerase activity, allowing them to proliferate indefinitely in a controlled manner.

References

- Telomere structure and telomerase in health and disease (review).

Genetics	General Principles	Aging
Subject	System	Topic

A healthy 31-year-old woman comes to the office as she and her husband desire a second child. The husband is infertile and the patient's son, who was conceived via donor insemination, was recently diagnosed with glycogen storage disease type II (Pompe disease). This rare autosomal recessive disease is known to affect 1 in 40,000 of the general population. Genetic testing confirms that the patient is a carrier for the disease. A different sperm donor is selected with no personal or family history of Pompe disease; however, his carrier status is unknown. What is the probability of the patient having an affected child with the new sperm donor?

- A. 1/4
- B. 1/240
- C. 1/400
- D. 1/800
- E. 1/40,000
- F. 1/160,000

Submit

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- A. 1/4 (9%)
- B. 1/240 (2%)
- ✓ C. 1/400 (23%)
- D. 1/800 (18%)
- E. 1/40,000 (14%)
- F. 1/160,000 (31%)

Omitted
Correct answer
C

23%
Answered correctly

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03/15/2020
Last Updated

Explanation

Hardy-Weinberg analysis

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Hardy-Weinberg analysis	
Allele frequency	$p + q = 1$ p: Normal allele frequency; q: Mutant allele frequency; 1: Total
Phenotypic frequency	$p^2 + 2pq + q^2 = 1$ p^2: Frequency of normal individuals; $2pq$: Carrier frequency; q^2: Frequency of diseased individuals; 1: Total
Calculating mutant allele frequency from disease prevalence	$\sqrt{q^2} = q$ q^2: Disease prevalence; q: Mutant allele frequency

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To be affected by an autosomal recessive disorder, an offspring must inherit 2 copies of the mutant allele (a), a copy from the mother and another copy from the father (in this case, the sperm donor).

In this example, genetic analysis confirms that the **mother is a carrier** (Aa), which gives her a **50%** chance of passing 1 mutant allele (a) to her child.

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To be affected by an autosomal recessive disorder, an offspring must inherit 2 copies of the mutant allele (a), a copy from the mother and another copy from the father (in this case, the sperm donor).

In this example, genetic analysis confirms that the **mother is a carrier** (Aa), which gives her a **50%** chance of passing 1 mutant allele (a) to her child.

The **sperm donor** does not have Pompe disease, but his **carrier status is unknown** (ie, he has either an AA or Aa genotype). Given that he has no family history of the disease, his risk of being a carrier is the same as that of the general population. **Hardy-Weinberg analysis** can be used to estimate the frequency of alleles and genotypes in the general population:

- The total gene pool is given by $(p + q) = 1$. By convention, p = normal allele (A) frequency and **q = mutant allele (a) frequency** in the population of interest.
- Disease frequency is equivalent to the proportion of homozygous recessive individuals. These affected individuals have 2 copies of the mutant allele (aa); therefore, the frequency of affected individuals = $q \times q = q^2$.
- **Carrier frequency** is equal to the proportion of heterozygous individuals. Carriers have only 1 mutant allele that may be inherited in 2 different ways (ie, Aa or aA); consequently, the probability of being a carrier = $2pq$. For rare autosomal recessive disorders, $p \approx 1$; therefore, the probability approximates to 2 times the frequency of the mutant allele, or **$2q$**.

In this case, 1 in 40,000 individuals is affected by the condition in the general population, so $q^2 = 1/40{,}000$ and $q = 1/\sqrt{40{,}000} = 1/200$. Thus, the probability of the **sperm donor** being a carrier = $2q = 2 \times (1/200)$ = **1/100**. Given that a carrier sperm donor would have a **50%** chance of passing on the mutant allele (a), the probability of the child being affected is:

P (mother gives recessive allele) × P (donor is a carrier) × P (donor gives recessive allele) = (1/2 × 1/100 ×1/2) = **1/400**

(Choices E and F) 1/40,000 represents the disease frequency (q^2), not the mutant allele frequency (q).

Educational objective:
The Hardy-Weinberg equation can be used to estimate carrier frequency, disease frequency, and frequency of different genotypes if at least 1 of these values is known.

- The total gene pool is given by $(p + q) = 1$. By convention, p = normal allele (A) frequency and **q = mutant allele (a) frequency** in the population of interest.
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References

- A century of Hardy-Weinberg equilibrium.
- Prevalence estimation for monogenic autosomal recessive diseases using population-based genetic data.

Genetics	Biostatistics & Epidemiology	Autosomal recessive inheritance
Subject	System	Topic

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A 24-year-old woman comes to the office after discovering a new mole on her right leg. She is worried that it might be skin cancer as she has used tanning beds several times a year since age 18. Physical examination shows a 5-mm brown, oval macule on her anterior thigh with a homogeneous coloration and discrete borders. The lesion appears darker than her other moles. A biopsy of the lesion shows normal-appearing nevus cells clustered in the epidermis, and she is diagnosed with a benign acquired melanocytic nevus. During histologic analysis, her epithelial cells are each found to contain a condensed body composed of heavily methylated DNA at the periphery of the nucleus. This region of DNA is most likely associated with which of the following genetic findings?

A. DNA supercoil accumulation

B. Extensive double-strand DNA break repair

C. Histone acetylation

D. Impaired mismatch repair

E. Low transcription activity

Submit

A 24-year-old woman comes to the office after discovering a new mole on her right leg. She is worried that it might be skin cancer as she has used tanning beds several times a year since age 18. Physical examination shows a 5-mm brown, oval macule on her anterior thigh with a homogeneous coloration and discrete borders. The lesion appears darker than her other moles. A biopsy of the lesion shows normal-appearing nevus cells clustered in the epidermis, and she is diagnosed with a benign acquired melanocytic nevus. During histologic analysis, her epithelial cells are each found to contain a condensed body composed of heavily methylated DNA at the periphery of the nucleus. This region of DNA is most likely associated with which of the following genetic findings?

- A. DNA supercoil accumulation (6%)
- B. Extensive double-strand DNA break repair (7%)
- C. Histone acetylation (9%)
- D. Impaired mismatch repair (4%)
- ✓ E. Low transcription activity (71%)

Omitted
Correct answer
E

71%
Answered correctly

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05/24/2020
Last Updated

Explanation

Euchromatin and heterochromatin

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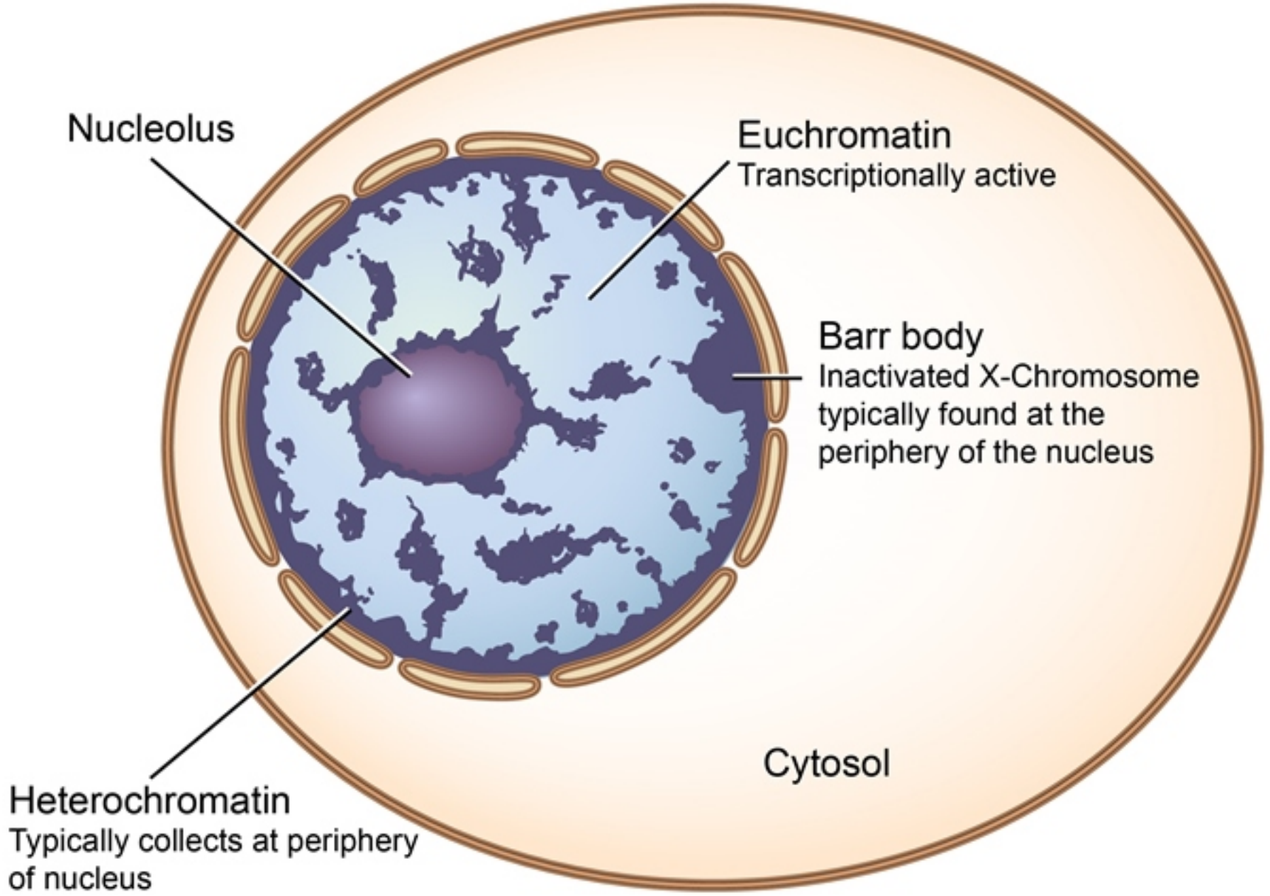
Euchromatin and heterochromatin



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In genetically normal (46,XX) females, one X chromosome is normally randomly deactivated in each cell during early embryonic development. **X-inactivation (lyonization)** is maintained across cell division, resulting in clusters of cells throughout the body that express either the maternal or paternal X chromosome. This mosaic pattern of X-chromosome expression generally prevents X-linked recessive conditions from manifesting in female carriers. However, in rare cases, skewed lyonization (uneven inactivation of maternal/paternal X chromosome due to chance alone) may result in females developing an X-linked recessive condition (eg, classic hemophilia).

The process of lyonization converts the inactive X chromosome into condensed **heterochromatin**, which can be identified on microscopy as a compact body at the periphery of the nucleus (**Barr body**). Heterochromatin consists of heavily **methylated DNA** (eg, cytosine converted to methylcytosine) and **deacetylated histones**, which cause it to have a low level of transcriptional activity **(Choice C)**. A small proportion of genes remain transcriptionally active on the inactivated X chromosome. For this reason, inheritance of an abnormal number of X chromosomes can cause clinical manifestations due to a gene-dosage effect, as seen with Turner (45,XO) and Klinefelter (47,XXY) syndromes.

(Choice A) During DNA replication, positive supercoiling occurs in the region ahead of the replication fork and must be removed for DNA replication to proceed. Topoisomerases reduce DNA supercoiling by nicking the DNA strands, introducing negative coiling, and religating the strands.

(Choice B) Double-strand DNA breakage can occur following exposure to ionizing radiation. Compared to single-strand breakage, double-stranded breaks are more prone to result in faulty repair, leading to mutations, malignancy, or cell death.

(Choice D) Repair of mismatched bases occurs throughout the genome during DNA replication. Impaired mismatch repair is associated with hereditary nonpolyposis colorectal cancer.

Educational objective:
X-inactivation occurs in genetically normal females and results in conversion of the inactivated X chromosome into compact heterochromatin (Barr body). Heterochromatin is condensed chromatin composed of heavily methylated DNA in tight association with deacetylated histones. It has a low level of transcriptional activity. In contrast, euchromatin is loosely arranged and exhibits a high level of transcriptional activity.

Genetics General Principles Dna structure & function

paternal X chromosome. This mosaic pattern of X-chromosome expression generally prevents X-linked recessive conditions from manifesting in female carriers. However, in rare cases, skewed lyonization (uneven inactivation of maternal/paternal X chromosome due to chance alone) may result in females developing an X-linked recessive condition (eg, classic hemophilia).

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Genetics	General Principles	Dna structure & function
Subject	System	Topic

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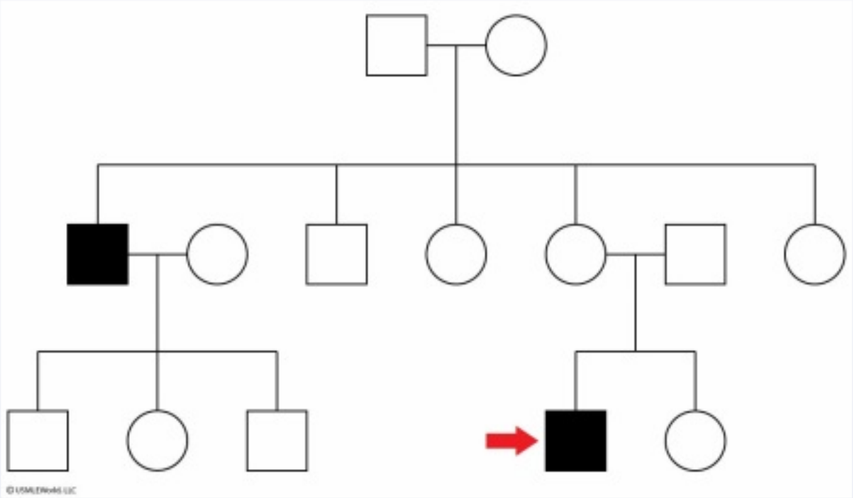
A 25-year-old man experiences severe intolerance to certain medications. On 2 occasions, his reactions to various drugs have necessitated hospital admission. His family pedigree with respect to this condition is shown below, with the red arrow indicating his position within the family.



Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

A. Autosomal dominant
B. Autosomal recessive
C. X-linked dominant
D. X-linked recessive
E. Mitochondrial

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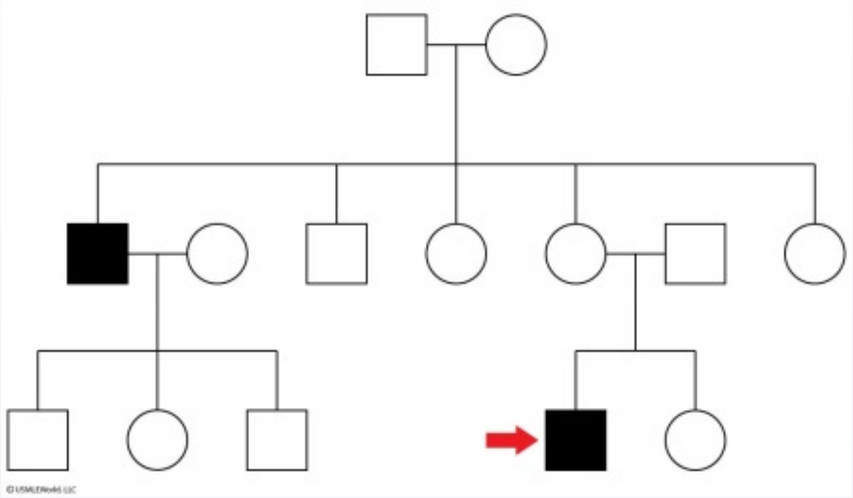

Assuming that the genetic condition demonstrates complete penetrance and is rare in the general population, which of the following inheritance patterns is most likely?

A. Autosomal dominant (1%)
B. Autosomal recessive (15%)
C. X-linked dominant (4%)
✓ D. X-linked recessive (75%)
E. Mitochondrial (3%)

Omitted
Correct answer

75%
Answered correctly

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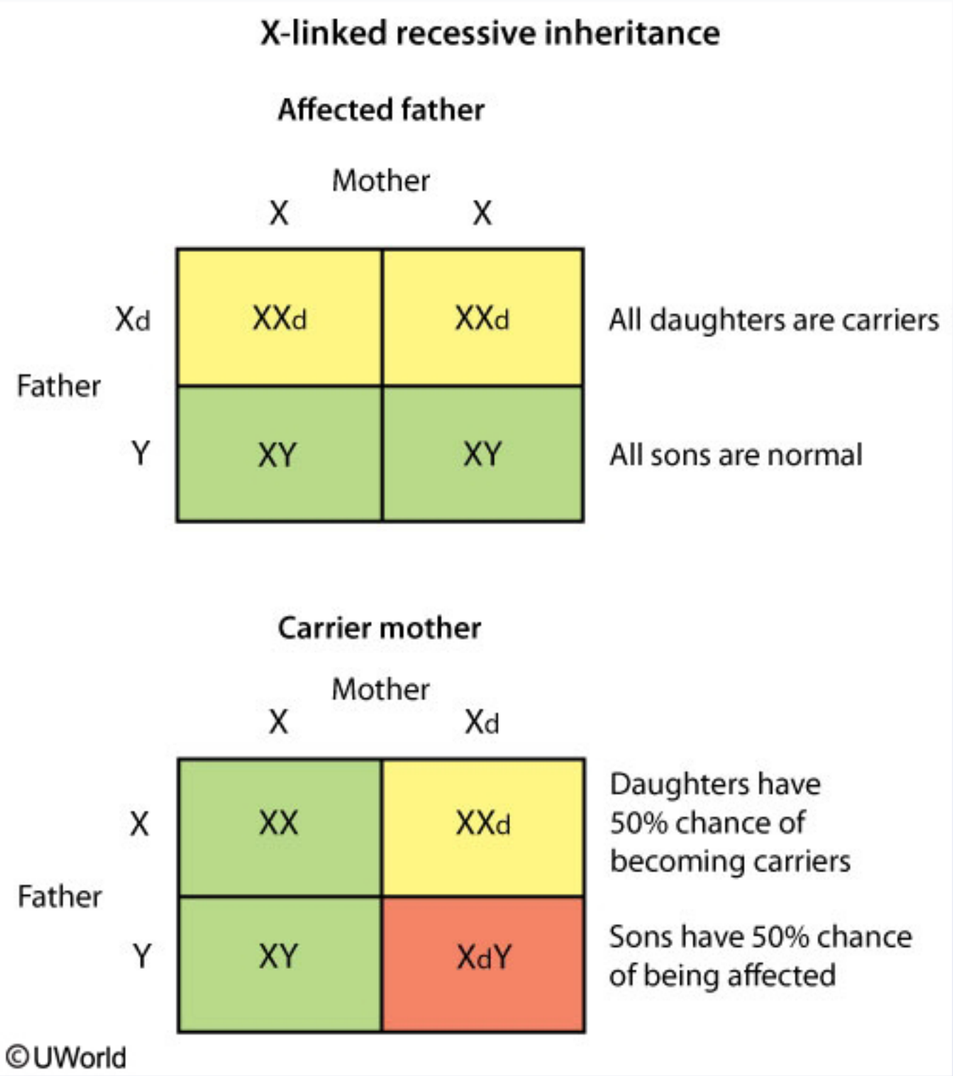
Last Updated



The pedigree shows that only males are affected by the drug intolerance. Specifically, **male offspring of unaffected parents** are affected. There is no evidence of male-to-male transmission. This pattern is most consistent with X-linked recessive inheritance from an asymptomatic carrier.

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The pedigree shows that only males are affected by the drug intolerance. Specifically, **male offspring of unaffected parents** are affected. There is no evidence of male-to-male transmission. This pattern is most consistent with X-linked recessive inheritance from an asymptomatic carrier female in the first generation. In **X-linked recessive inheritance**:

1. Affected males will always produce unaffected sons and carrier daughters.
2. Carrier females have a 50% chance of producing an affected son or carrier daughter.

G6PD deficiency, which causes acute hemolytic anemia on exposure to oxidant drugs, follows an X-linked recessive pattern of inheritance.

(Choice A) With autosomal dominant inheritance, affected individuals have at least 1 parent that is also affected.

(Choice B) In autosomal recessive inheritance, both parents must at least be carriers (heterozygous) for the mutation in order to produce affected offspring. However, the father of the marked individual comes from *outside the family* and would be unlikely to carry the mutation (the question states the mutation is rare in the general population).

(Choice C) In X-linked dominant inheritance, affected individuals have at least 1 parent (of either sex) that is also affected. An affected male will always produce affected daughters, but none of his sons will be affected.

(Choice E) Conditions with mitochondrial inheritance are transmitted only by females. All of an affected female's offspring are likely to show signs of the disease.

Educational objective:
In X-linked recessive inheritance 1) affected males will always produce *unaffected* sons and *carrier* daughters, and 2) carrier females have a 50% chance of producing *affected* sons and *carrier* daughters. G6PD deficiency follows this inheritance pattern and causes acute hemolytic anemia in response to oxidant drugs.

Genetics	General Principles	X linked inheritance
Subject	System	Topic

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Exhibit Display

X-linked dominant inheritance

Affected father

Father \ Mother	X	X
Xd	XXd	XXd
Y	XY	XY

All daughters are affected

All sons are normal

Affected mother

Father \ Mother	X	Xd
X	XX	XXd
Y	XY	XdY

All sons & daughters have 50% chance of being affected

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A 14-year-old girl is brought to the office for a routine physical examination. The patient will be starting her freshman year of high school soon. She plays the clarinet in the school band but does not play any sports. The patient says that she is not sexually active and does not use tobacco, alcohol, or illicit drugs. Height is at the 5th percentile, and weight is at the 25th percentile. Her temperature is 36.7 C (98 F), blood pressure is 120/80 mm Hg, pulse is 88/min, and respirations are 16/min. Physical examination shows a short and thick neck, a broad chest, and shortened fourth metacarpals bilaterally. A murmur is heard on cardiac auscultation. Which of the following would most likely be seen in an echocardiogram?

A. Atrial septal defect
B. Bicuspid aortic valve
C. Mitral stenosis
D. Mitral valve prolapse
E. Patent ductus arteriosus
F. Ventricular septal defect

Submit

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- A. Atrial septal defect (5%)
- ✓ B. Bicuspid aortic valve (76%)
- C. Mitral stenosis (1%)
- D. Mitral valve prolapse (4%)
- E. Patent ductus arteriosus (7%)
- F. Ventricular septal defect (5%)

Omitted
Correct answer
B

76%
Answered correctly

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Explanation

Bicuspid aortic valve disease

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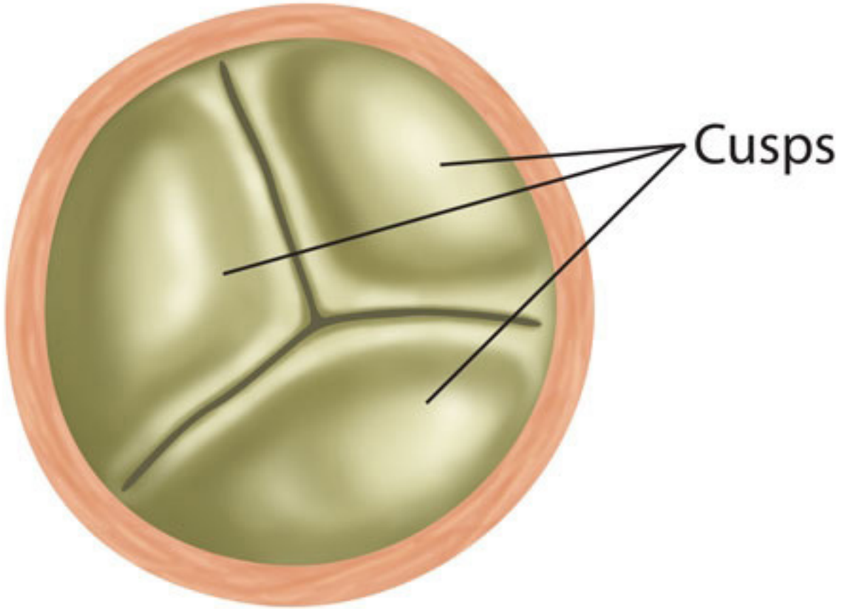
Bicuspid aortic valve disease

Normal aortic valve



Bicuspid

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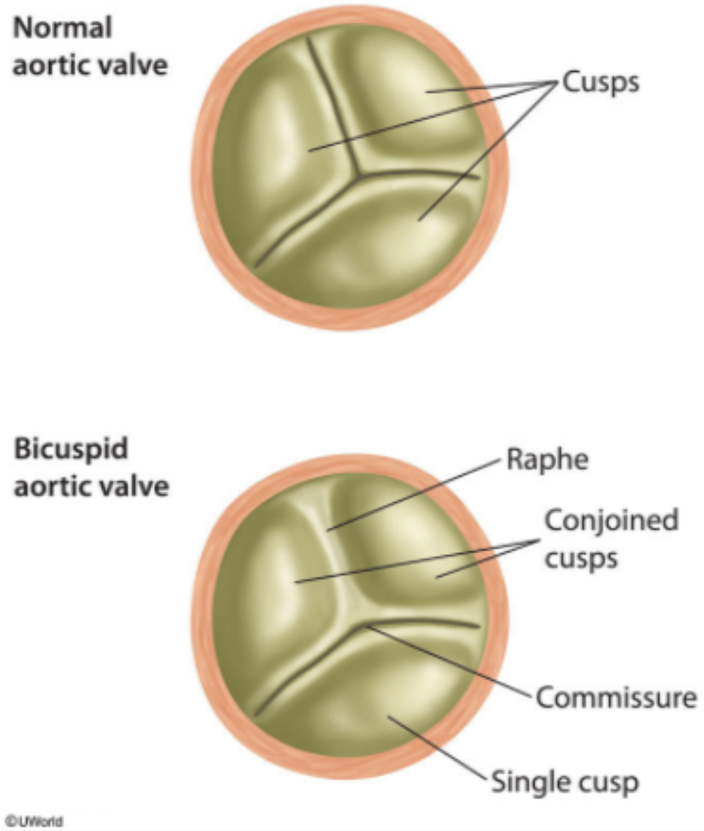
Exhibit Display

Bicuspid aortic valve disease



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This patient's short stature, short and thick neck, broad chest, and shortened fourth metacarpals are characteristic of Turner syndrome (TS). **Bicuspid aortic valve** is the most common congenital cardiac malformation in patients with TS. It is usually an isolated abnormality; however, it may occur in combination with other anomalies, particularly aortic coarctation. A nonstenotic bicuspid aortic valve manifests with an aortic ejection sound, which is an **early systolic, high-frequency click** heard over the **right second interspace**. As the valve calcifies, it may result in progressive valvular dysfunction, manifesting with aortic stenosis or regurgitation and associated murmurs. Patients with a bicuspid aortic valve are susceptible to infectious endocarditis due to abnormal leaflet structure and turbulent flow.

(Choices A and F) Complete atrioventricular canal, atrial septal defect (ASD), and ventricular septal defect (VSD) are the most common cardiac anomalies in Down syndrome. Fixed splitting of the second heart sound is characteristically heard with an ASD, whereas VSDs produce a holosystolic murmur at the left lower sternal border.

(Choice C) Mitral stenosis is seen in rheumatic heart disease. It produces a mid-diastolic, low-pitched, rumbling murmur that may begin with an opening snap.

(Choice D) A mid-systolic click, often accompanied by a late systolic murmur, is the hallmark of mitral valve prolapse (MVP). MVP is more common in connective tissue disorders such as Marfan and Ehlers-Danlos syndromes.

(Choice E) Patent ductus arteriosus (PDA) produces a continuous, machinelike murmur during both systole and diastole. PDA is common in premature infants, especially those with respiratory distress syndrome. A PDA may also be seen in an infant with coarctation of the aorta but is less likely in older patients.

Educational objective:
Turner syndrome is associated with congenital anomalies of the aorta, and the most common defect is a bicuspid aortic valve. A nonstenotic bicuspid aortic valve can manifest as an early systolic, high-frequency click over the right second interspace. Bicuspid aortic valves are at risk for stenosis, insufficiency, and infection.

References

- Turner syndrome: diagnosis and management.

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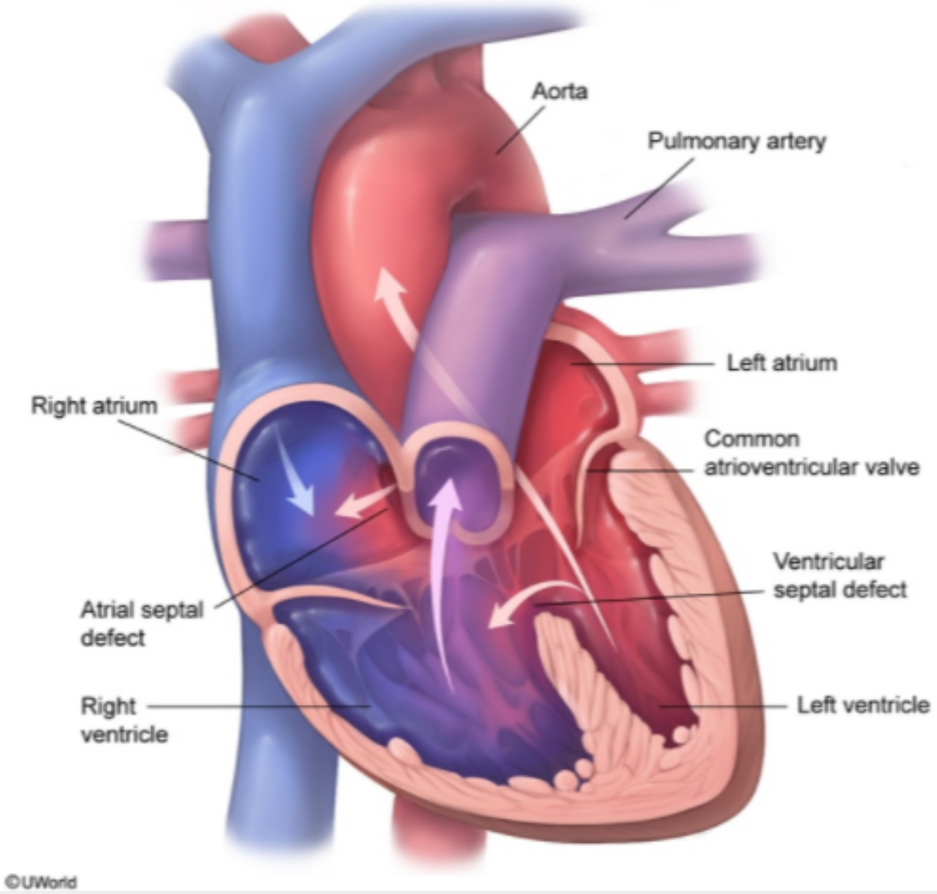
Complete atrioventricular canal defect



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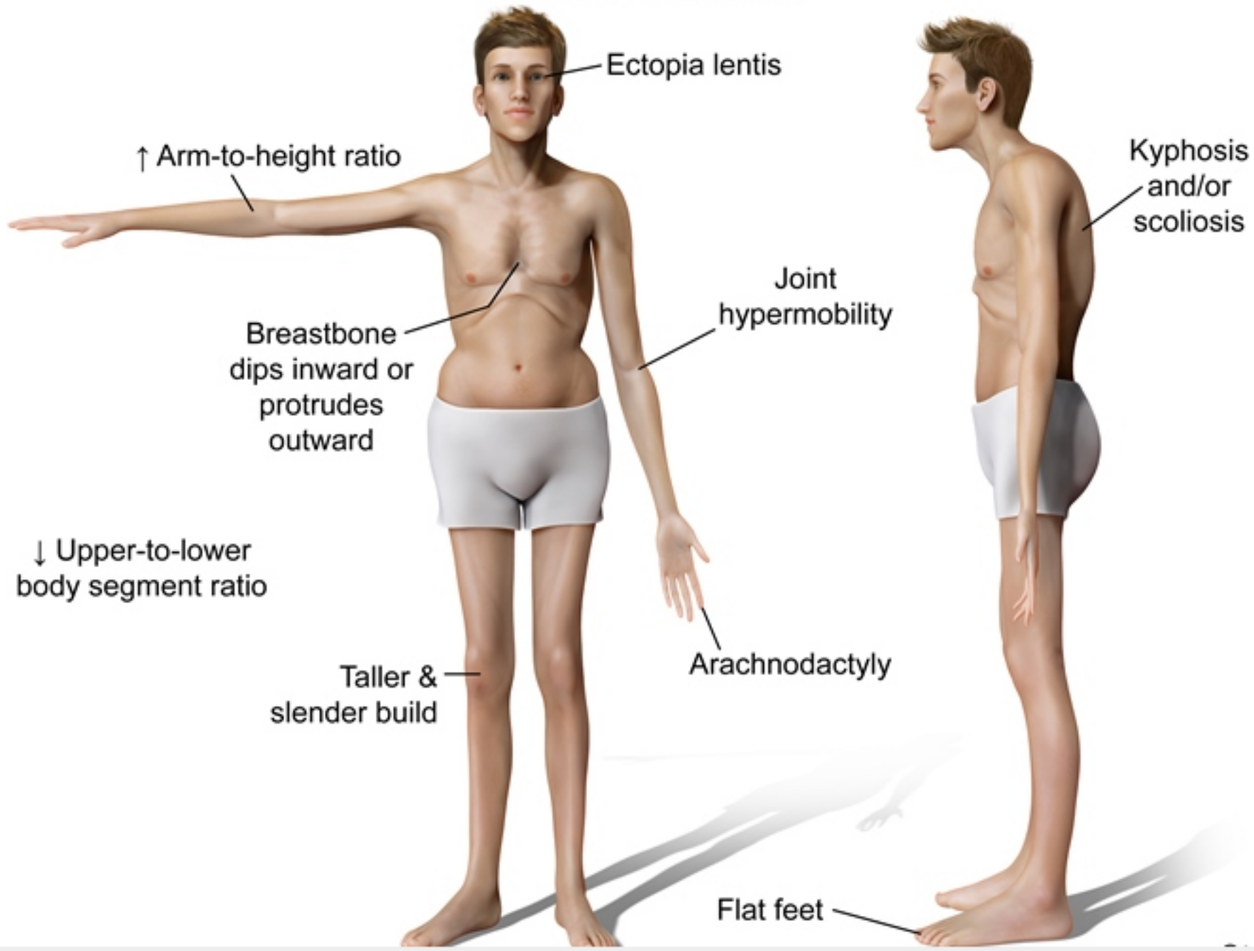

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References

- Turner syndrome: diagnosis and management.
- Aortic valve disease in Turner syndrome.

Genetics	Cardiovascular System	Turner syndrome
Subject	System	Topic

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Studies conducted following an influenza epidemic that affected the inhabitants of several countries determine that the cause is an antigenically novel virus strain carrying the animal-strain hemagglutinin and neuraminidase surface molecules. Further analysis reveals that reassortment of the genetic materials occurred during coinfection with human influenza virus and swine influenza virus, leading to the development of some progeny that contain genetic materials from both viruses. Which of the following viruses can undergo a similar process?

A. Hepatitis C virus

B. Human papillomavirus

C. Measles virus

D. Poliovirus

E. Rotavirus

Submit

Studies conducted following an influenza epidemic that affected the inhabitants of several countries determine that the cause is an antigenically novel virus strain carrying the animal-strain hemagglutinin and neuraminidase surface molecules. Further analysis reveals that reassortment of the genetic materials occurred during coinfection with human influenza virus and swine influenza virus, leading to the development of some progeny that contain genetic materials from both viruses. Which of the following viruses can undergo a similar process?

- A. Hepatitis C virus (19%)
- B. Human papillomavirus (9%)
- C. Measles virus (10%)
- D. Poliovirus (5%)
- ✓ E. Rotavirus (55%)

Omitted
Correct answer
E

55%
Answered correctly

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02/26/2020
Last Updated

Explanation

Reassortment (segmented viruses)

Virus A Virus B

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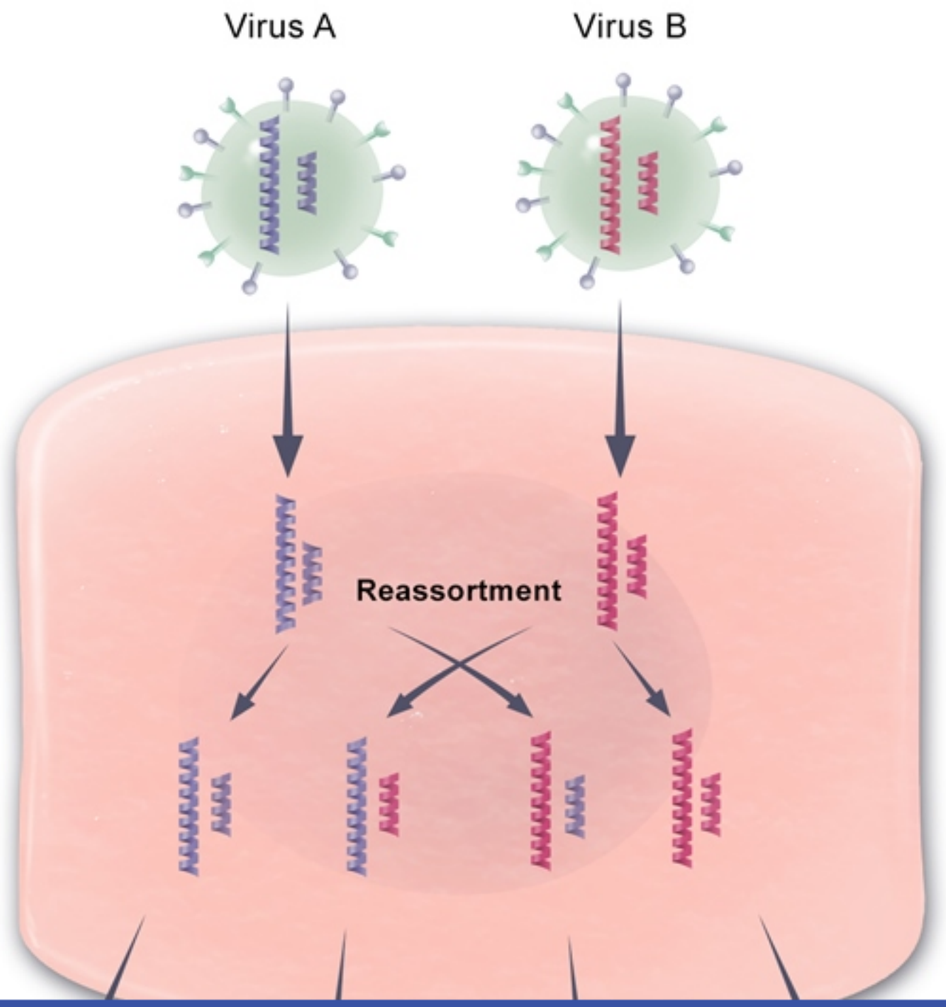
Reassortment (segmented viruses)



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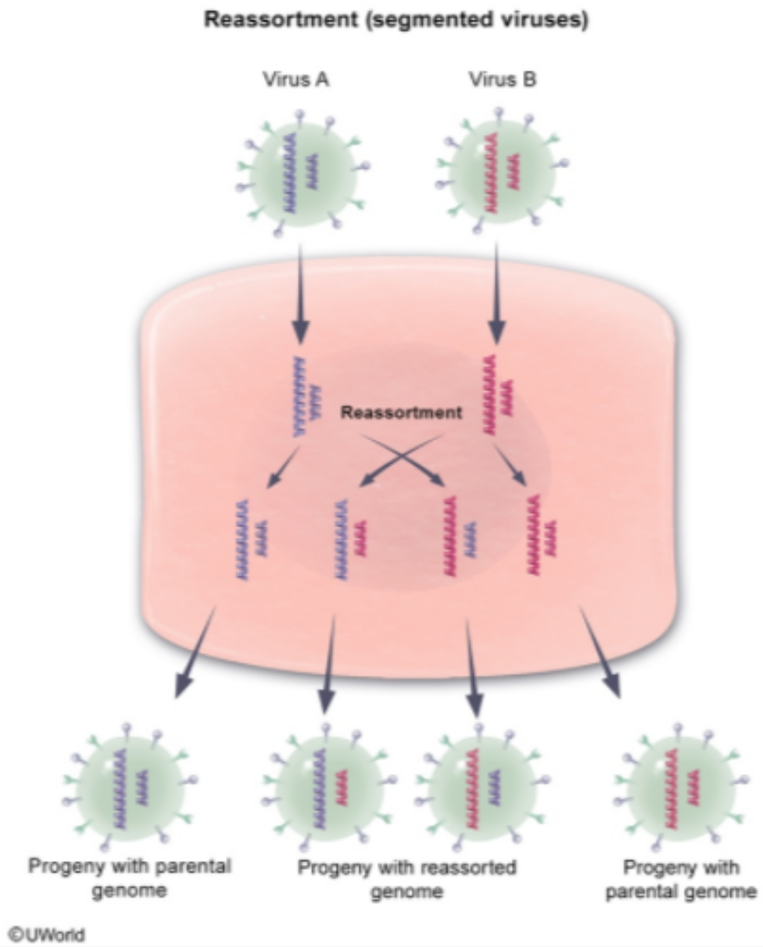

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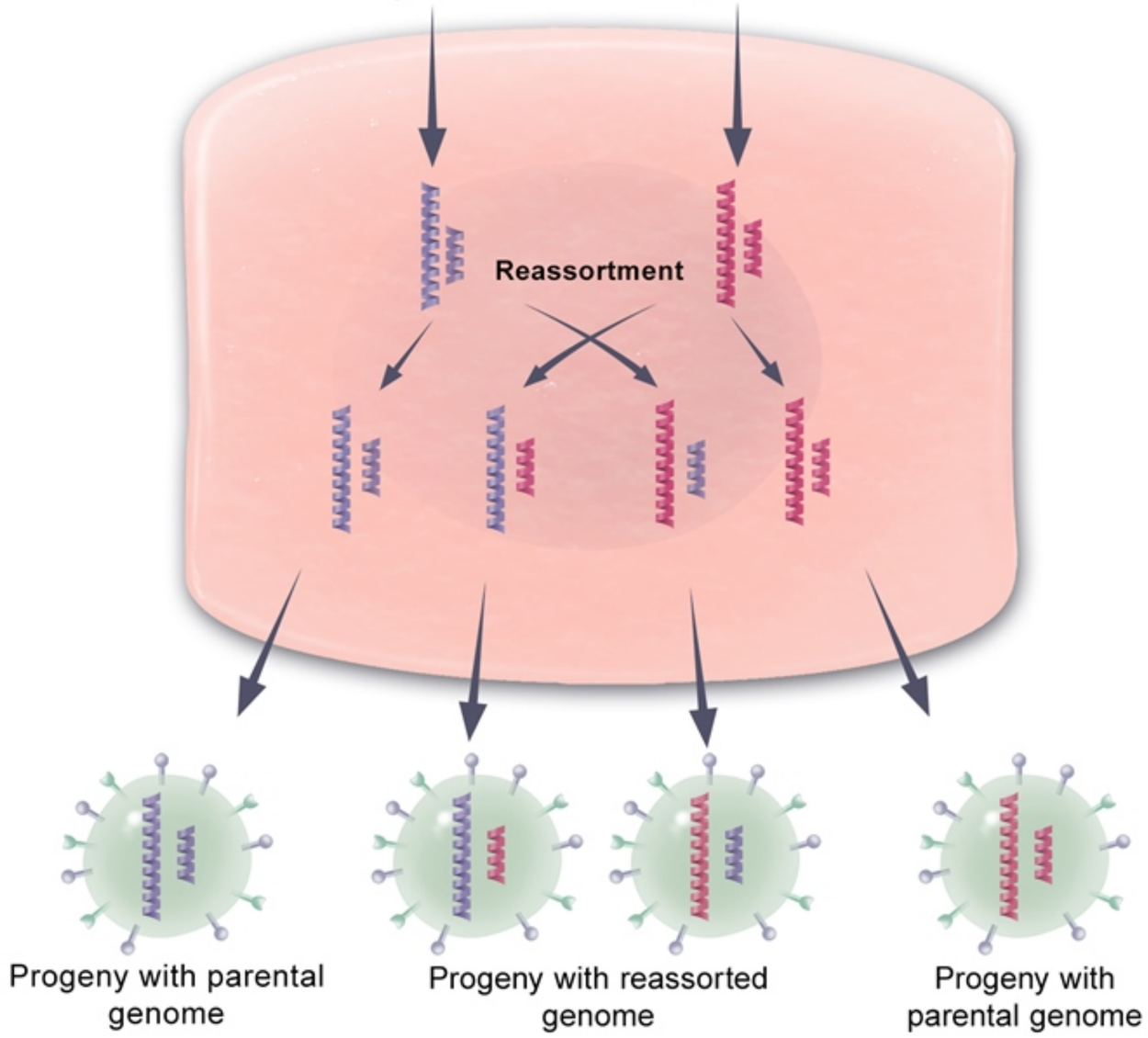

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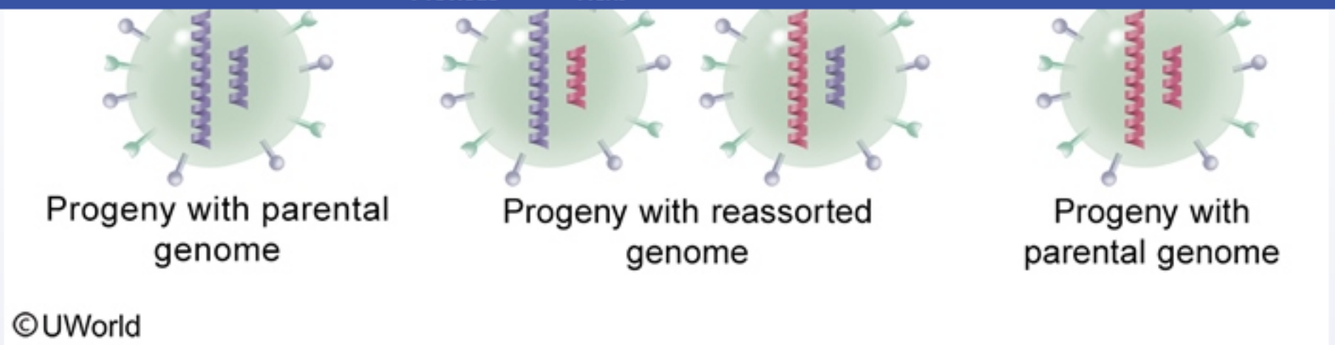

Genetic shift in the influenza A virus involves **reassortment** of genomic segments of the **human** strain with genomic segments of the **animal** strain, typically when both strains coinfect birds (avian) or pigs (swine). The resulting new strain can cause a new influenza epidemic or pandemic if it has dramatically altered viral surface glycoproteins (eg, hemagglutinin).

The key structural feature that enables influenza viruses to undergo such relatively rapid genetic shifts through reassortment is the **segmented** nature of their genomes. Members of another virus family with a segmented genome could also undergo such reassortment - as opposed to the less radical, slower genetic drift that occurs via point mutations in all viral families. Among the viruses listed, only **rotavirus** has a segmented genome. Segmented viruses include orthomyxoviruses, reoviruses, bunyaviruses, and arenaviruses.

(Choices A, B, C, and D) Hepatitis C virus, human papillomavirus, measles virus, and poliovirus all lack the segmented genome necessary to undergo reassortment.

Educational objective:
Viruses with segmented genomes (eg, orthomyxoviruses, rotaviruses) are capable of genetic shifts through reassortment. Reassortment (genetic shift) involves exchange of entire genomic segments, a far more dramatic process than the point mutations responsible for genetic drift.

Genetics	Infectious Diseases	Viral genetics
Subject	System	Topic

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A 12-year-old boy is evaluated in the clinic due to excessive bleeding following a tooth extraction. The patient also develops large bruises after only minor injury but has had no major bleeding episodes in the past. His maternal uncle died from an intracranial hemorrhage. Laboratory testing reveals decreased coagulation factor VIII activity levels. A referral is made to a clinical geneticist, who suspects that the patient has a deletion mutation in the enhancer sequence of the factor VIII gene. This mutation has resulted in decreased transcription of factor VIII by RNA polymerase II. Which of the following is the most accurate statement regarding the abnormal genetic sequence in this patient?

A. It can be located upstream, downstream, or within introns of the gene

B. It can function within only a short distance of the gene

C. It directly binds RNA polymerase and general transcription factors

D. It does not require protein binding to affect transcription

E. It is required to initiate transcription

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- ✓ A. It can be located upstream, downstream, or within introns of the gene (61%)
- B. It can function within only a short distance of the gene (7%)
- C. It directly binds RNA polymerase and general transcription factors (14%)
- D. It does not require protein binding to affect transcription (4%)
- E. It is required to initiate transcription (12%)

Omitted
Correct answer
A

61%
Answered correctly

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Explanation

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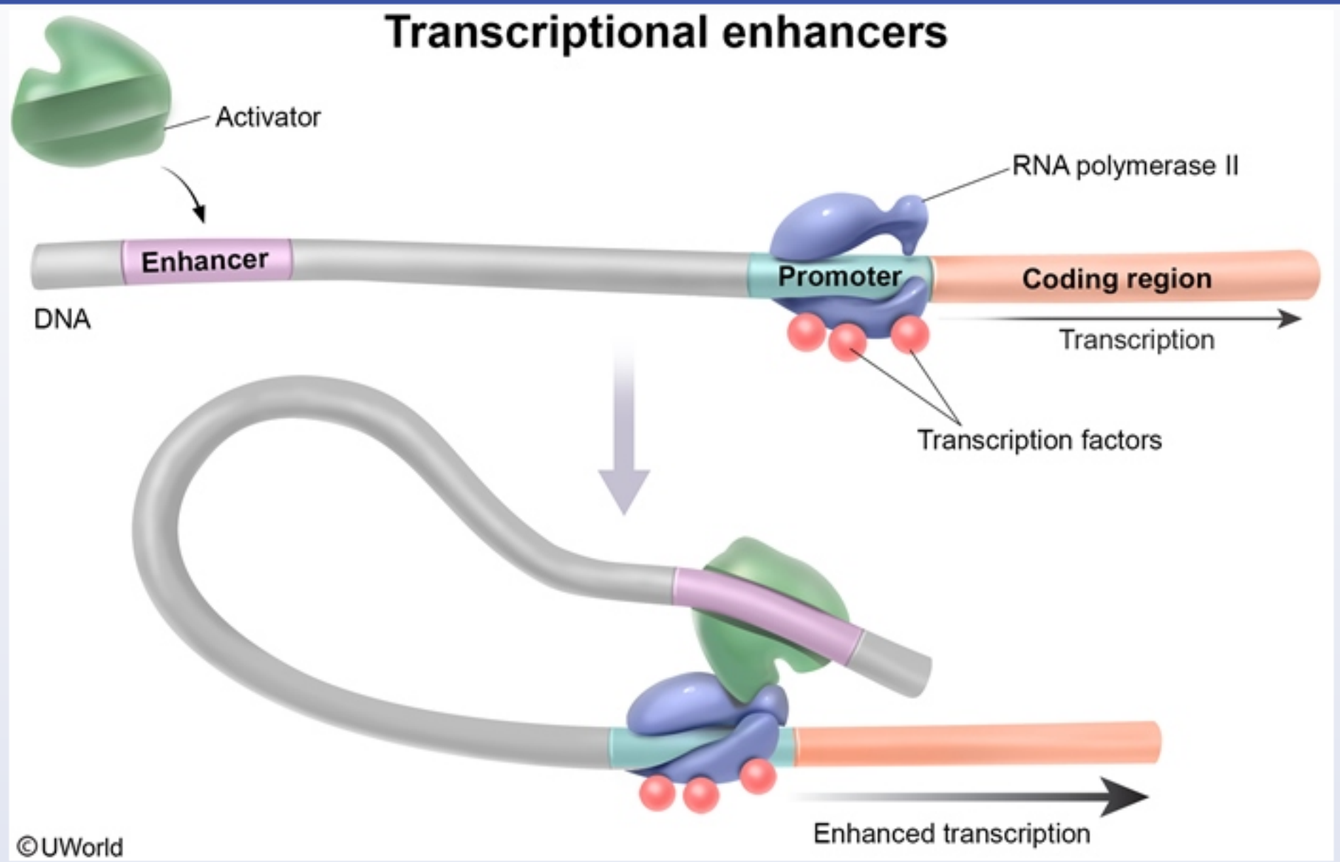

This patient has hemophilia A, an X-linked recessive disorder characterized by easy bruising and excessive bleeding due to a deficiency in coagulation factor VIII. The disorder can be caused by a variety of different mutations in the factor VIII gene, including deletions in the enhancer sequence.

In eukaryotic gene transcription, nuclear RNA polymerase II uses a DNA template to generate complementary mRNA, which is then processed and translated into protein. Eukaryotic genes have associated promoter and enhancer sequences that mediate transcription. Promoter sequences directly bind general transcription factors and RNA polymerase II upstream from the gene locus, which is necessary for the initiation of

This patient has hemophilia A, an X-linked recessive disorder characterized by easy bruising and excessive bleeding due to a deficiency in coagulation factor VIII. The disorder can be caused by a variety of different mutations in the factor VIII gene, including deletions in the enhancer sequence.

In eukaryotic gene transcription, nuclear RNA polymerase II uses a DNA template to generate complementary mRNA, which is then processed and translated into protein. Eukaryotic genes have associated promoter and enhancer sequences that mediate transcription. Promoter sequences directly bind general transcription factors and RNA polymerase II upstream from the gene locus, which is necessary for the initiation of transcription **(Choices C and E)**. There are 2 types of eukaryotic promoter regions: the TATA, or Hogness, box, which is located approximately 25 bases upstream from the gene being transcribed; and the CAAT box, which is 70-80 bases upstream from the gene.

In contrast to promoters, **enhancer sequences** bind activator proteins that facilitate bending of DNA. DNA bending allows activator proteins to interact with general transcription factors and RNA polymerase II at the promoter, increasing the **rate of transcription (Choice D)**. Enhancers can be located **upstream or downstream** from the gene being transcribed and may be near the gene or thousands of base pairs away **(Choice B)**. They have also been identified both **within introns** of the gene being transcribed as well as on separate chromosomes. Silencers are similar to enhancers, but they decrease transcription rates by binding repressor proteins.

Educational objective:
Enhancers and silencers may be located upstream, downstream, or within a transcribed gene; these gene sequences function to increase and decrease the rate of transcription, respectively. In contrast, promoter regions are typically located 25 or 75 bases upstream from their associated genes and function to initiate transcription.

References

- Regulatory regions in DNA: promoters, enhancers, silencers, and insulators.

Genetics	General Principles	Transcription
Subject	System	Topic

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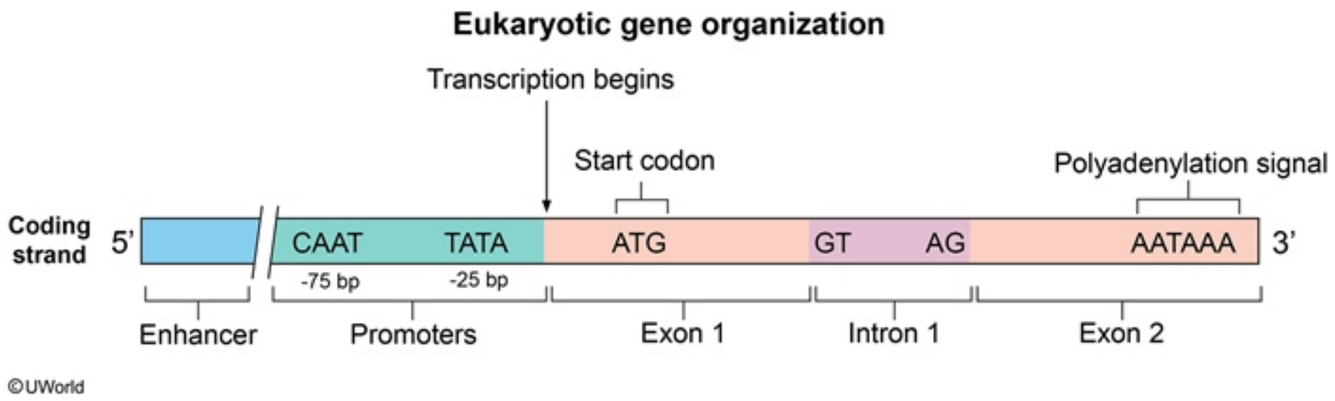

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A mutation in a non-coding DNA sequence is believed to affect expression of the gene coding for a specific fetal enzyme. Liver and bone marrow cells from the fetus and his parents are obtained. Which of the following is the best method to determine if this gene is being transcribed in cultures of the isolated cells?

A. Northern blot
B. Western blot
C. Southern blot
D. Southwestern blot
E. Enzyme-linked immunosorbent assay

Submit

A mutation in a non-coding DNA sequence is believed to affect expression of the gene coding for a specific fetal enzyme. Liver and bone marrow cells from the fetus and his parents are obtained. Which of the following is the best method to determine if this gene is being transcribed in cultures of the isolated cells?

- ✓ A. Northern blot (50%)
- B. Western blot (12%)
- C. Southern blot (25%)
- D. Southwestern blot (7%)
- E. Enzyme-linked immunosorbent assay (4%)

Omitted
Correct answer
A

50%
Answered correctly

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04/06/2020
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Explanation

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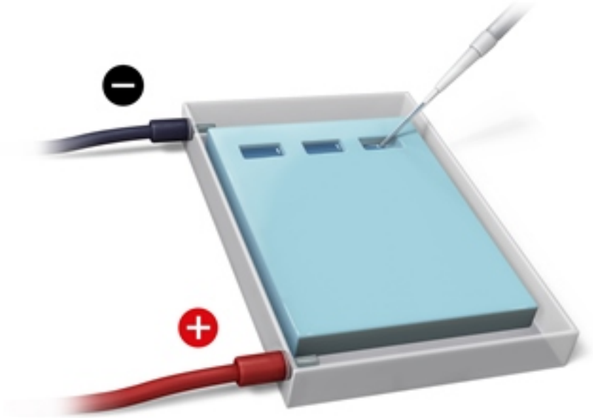
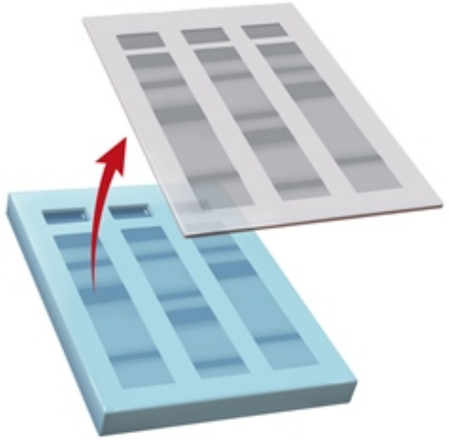
Northern blot

1. Load RNA samples onto gel and apply electric field



2. Transfer samples from gel to blotting membrane



3. Hybridize with probes and visualize results

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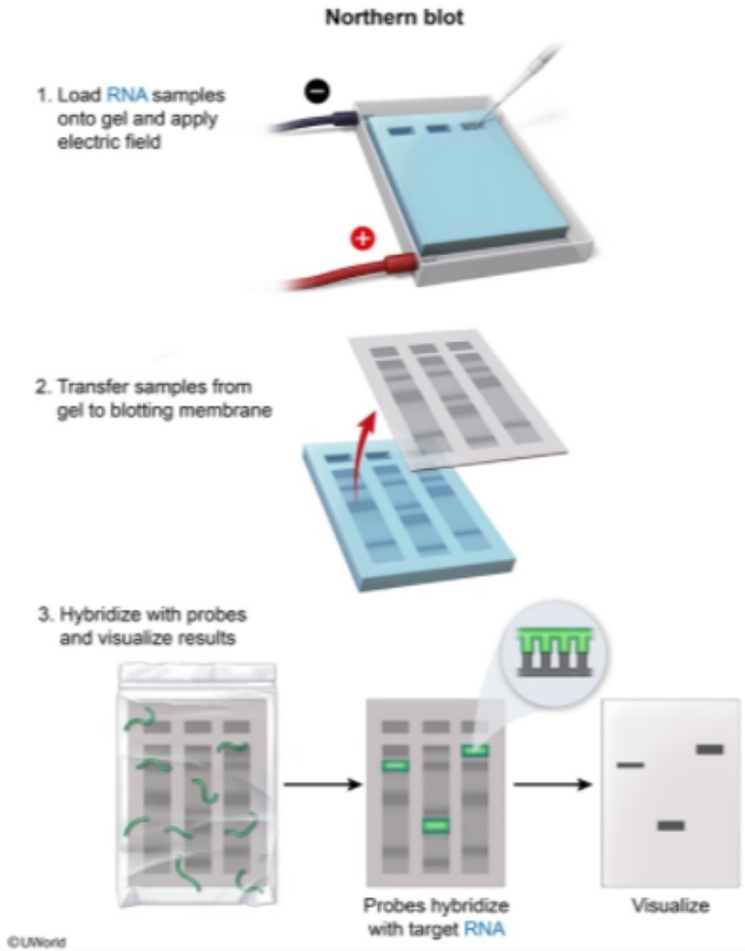

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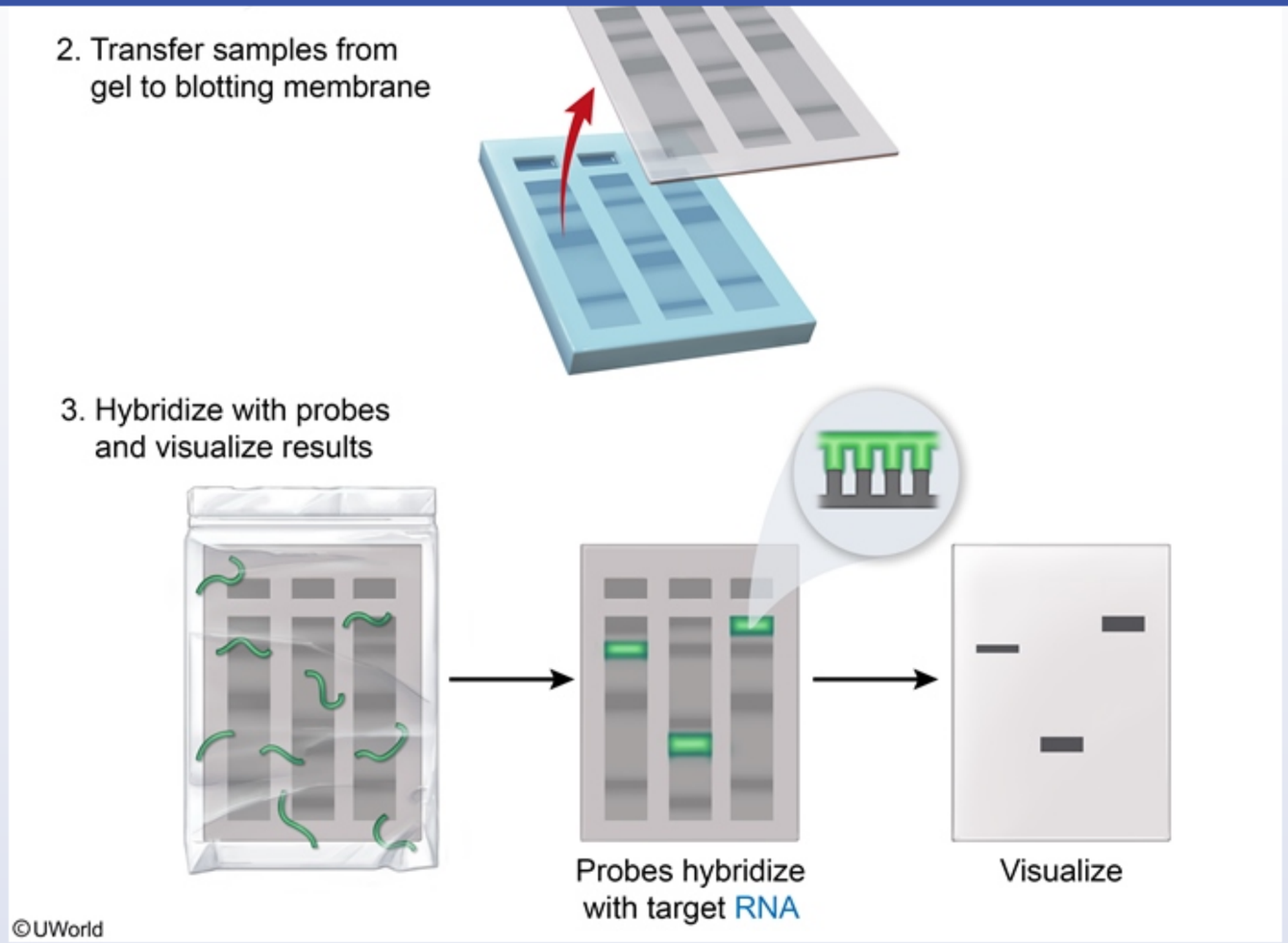

The Southern, Western, Northern and Southwestern blot procedures are techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The best method for determining whether a gene is undergoing **transcription** is to analyze for the presence of its **mRNA** using a **Northern blot**. In the case described above, Northern blot analysis of each of the cell culture samples can determine if mRNA corresponding to the gene of interest is being transcribed.

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All of the "blot" tests rely on the same basic techniques. First, the components of the unknown sample – DNA for Southern blots, mRNA for Northern blots, protein for Western blots, and DNA-bound protein for Southwestern blots – are separated by size and charge via gel electrophoresis. The resultant bands are then blotted onto a nitrocellulose membrane and incubated with a labeled hybridization probe or antibody to identify the specific DNA fragment, mRNA molecule or protein of interest.

(Choice B) A complete failure of gene expression would lead to a failure to produce the protein, which can be detected by Western blotting. However, the question is asking how to determine if the gene is being transcribed (genes may be transcribed but not properly expressed if there is a problem with protein translation). As transcription refers to the production of mRNA from a DNA template, a test that detects specific mRNA sequences (Northern blot) would be most appropriate.

(Choices C and D) This patient's mutation in a non-coding DNA sequence (likely affecting a promotor or enhancer region) is resulting in decreased gene expression. A Southern or Southwestern blot could potentially be used to detect the mutated DNA sequence and assess for transcription factor binding. However, the degree of transcription of the affected gene is better assessed through direct detection of its associated mRNA.

(Choice E) The ELISA (enzyme-linked immunosorbent assay) is a test commonly employed to measure the amount of a protein in body fluids. It can be quantitative, for example, to measure plasma insulin levels.

Educational objective:
Northern blots detect target mRNA in a sample and can be used to assess the degree of gene transcription.

Genetics	General Principles	Transcription
Subject	System	Topic

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An 18-year-old man comes to the office due to abnormal skin pigmentation and premature hair graying. His nails are also thin and break easily, and he has white patches on his tongue. The patient's father had similar features at a young age and died of progressive pulmonary fibrosis. Physical examination shows diffuse gray hair, areas of reticular hyperpigmentation on the torso, dystrophic nails, and oral leukoplakia. Genetic testing reveals a loss-of-function mutation affecting the telomerase reverse transcriptase gene. Which of the following cell types is likely to be most affected by this mutation?

A. Cardiac myocytes
B. CNS neurons
C. Compact bone osteocytes
D. Hematopoietic stem cells
E. Vascular endothelial cells

Submit

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- A. Cardiac myocytes (1%)
- B. CNS neurons (5%)
- C. Compact bone osteocytes (2%)
- ✓ D. Hematopoietic stem cells (79%)
- E. Vascular endothelial cells (10%)

Omitted
Correct answer
D

79%
Answered correctly

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02/11/2020
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Explanation

Effect of telomerase on cell division

Chromosome

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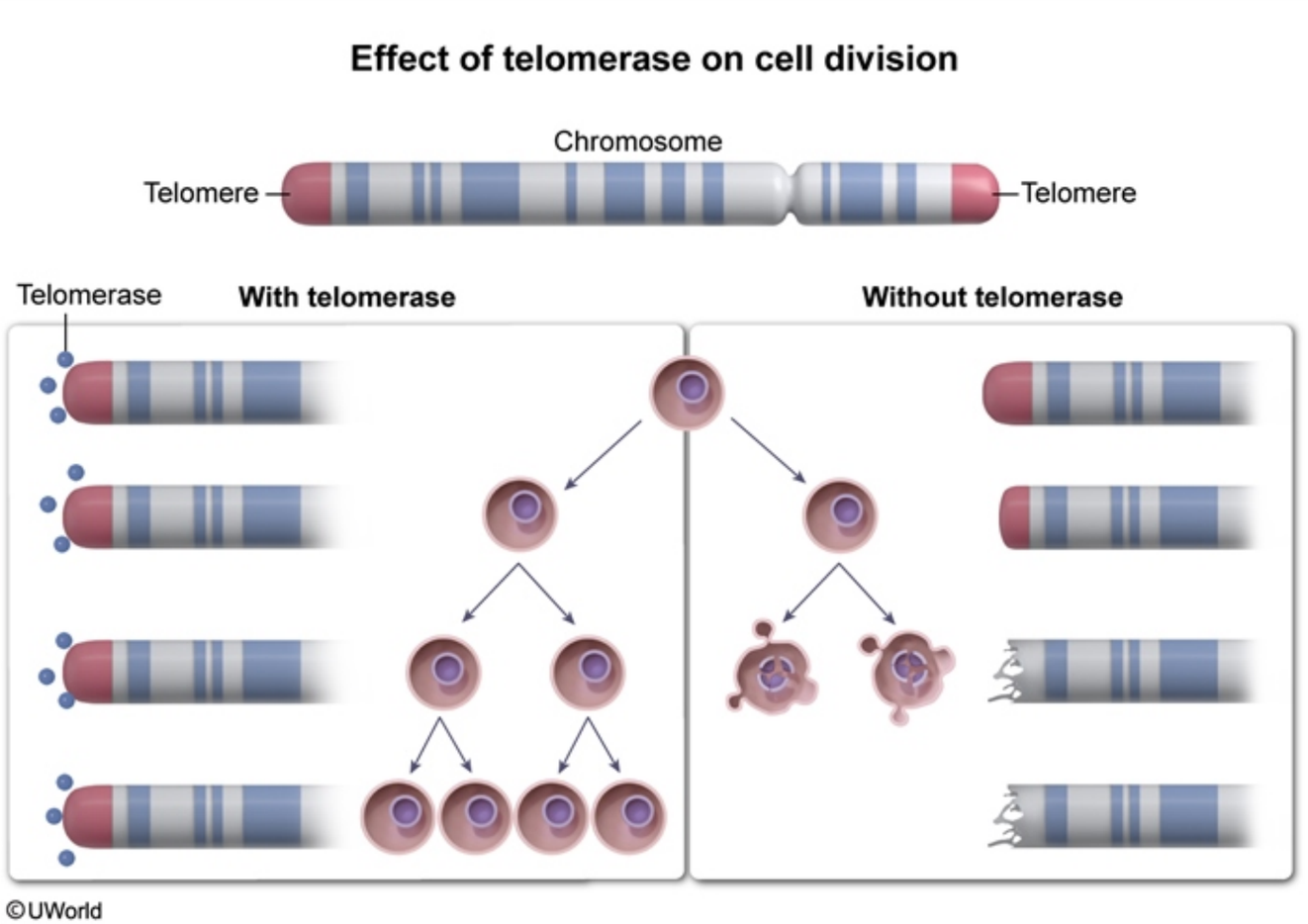

This patient has dyskeratosis congenita; a genetic disorder involving a mutation in the genes related to telomere maintenance (eg, telomerase reverse transcriptase) that results in short telomeres. **Telomeres** are a complex of protein (eg, shelterin) and DNA repeats (eg, TTAGGG) at the ends of chromosomes that **prevent chromosomal degradation** and fusion with neighboring chromosomes. With each cellular division telomeres progressively shorten, eventually reaching a critical length at which apoptosis or senescence is triggered.

In cells with a high turnover rate (eg, epithelial cells, lymphocytes, **hematopoietic stem cells**), telomere length is maintained by telomerase. This

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This patient has dyskeratosis congenita; a genetic disorder involving a mutation in the genes related to telomere maintenance (eg, telomerase reverse transcriptase) that results in short telomeres. **Telomeres** are a complex of protein (eg, shelterin) and DNA repeats (eg, TTAGGG) at the ends of chromosomes that **prevent chromosomal degradation** and fusion with neighboring chromosomes. With each cellular division telomeres progressively shorten, eventually reaching a critical length at which apoptosis or senescence is triggered.

In cells with a high turnover rate (eg, epithelial cells, lymphocytes, **hematopoietic stem cells**), telomere length is maintained by telomerase. This complex, composed of an RNA template and a reverse transcriptase, adds DNA repeats to the end of telomeres as they are lost with cell division. Without normal telomerase activity, rapidly dividing cells cannot maintain chromosomal integrity, triggering **premature cell death**. In patients with short telomere disorders, loss of these cells can cause characteristic mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), **bone marrow failure** (eg, pancytopenia), and pulmonary fibrosis (due to alveolar epithelial dysfunction).

(Choices A, B, C, and E) Telomerase is inactivated in long-lived, differentiated cells such as cardiac myocytes, CNS neurons, compact bone osteocytes, and vascular endothelial cells; therefore, these cells are not likely to be affected by this patient's mutation. However, in cancer cells derived from differentiated cells, telomerase is reactivated, allowing continuous cellular division without loss of telomere length.

Educational objective:
Telomeres help maintain chromosomal integrity and are preserved in rapidly dividing cell lines (eg, epithelial cells, lymphocytes, hematopoietic stem cells) by telomerase. Disorders involving telomerase function (eg, dyskeratosis congenita) result in premature death of cells with high turnover, characteristically causing mucocutaneous changes (eg, oral leukoplakia, dystrophic nails), bone marrow failure, and pulmonary fibrosis.

References

- Bone marrow failure and the telomeropathies.

Genetics	General Principles	Aging
Subject	System	Topic

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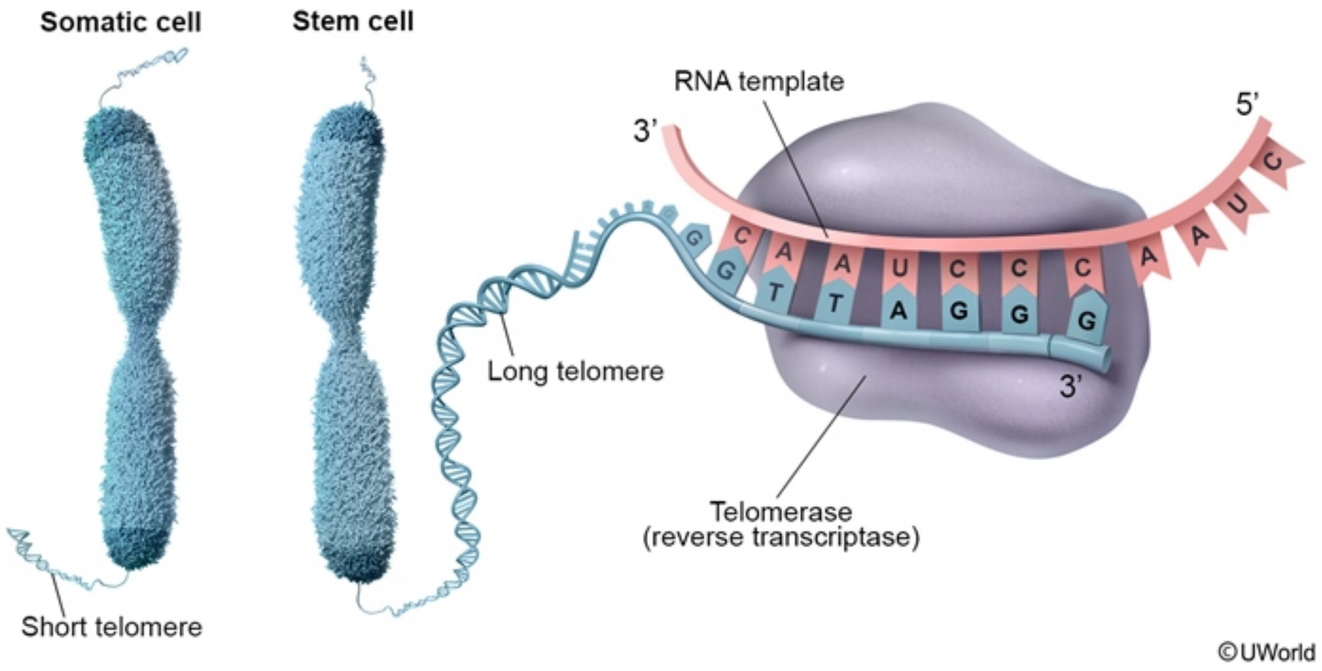

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A 19-year-old woman is evaluated for new onset generalized tonic-clonic seizures. For the past several years, she has also been having erratic jerks of her arms and legs, and intermittent muscle weakness. The girl has multiple family members with similar symptoms. Neurological examination reveals decreased sensation in the lower extremities and a broad-based gait. Skeletal muscle biopsy shows ragged, red-appearing muscle fibers. Further analysis reveals that the patient's symptoms are due to a mutation affecting extranuclear DNA. Which of the following pedigrees is most likely to represent this patient's family history? (The arrow points to the patient.)

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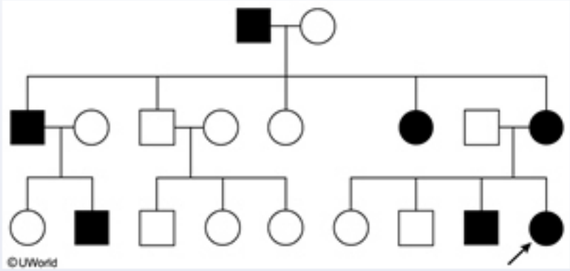

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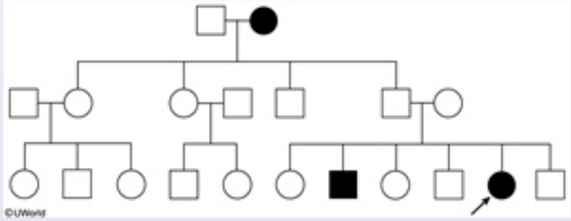

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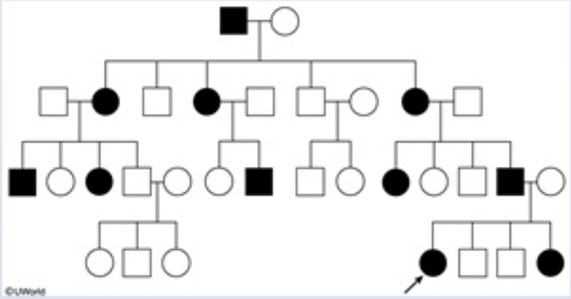

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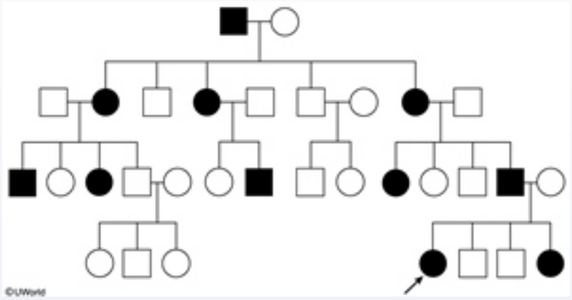

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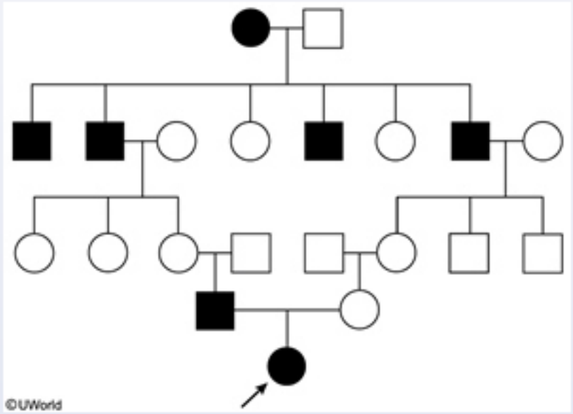

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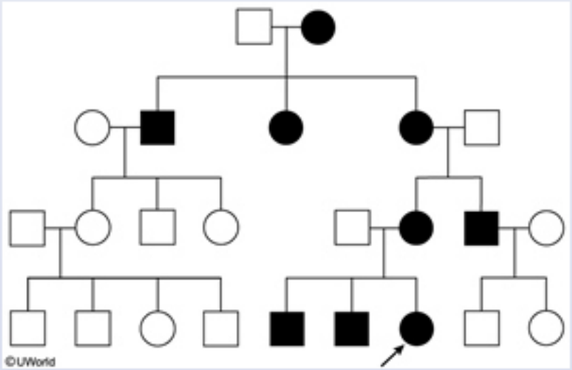

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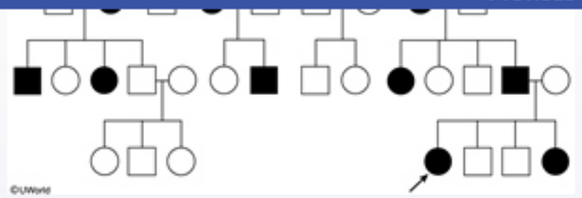
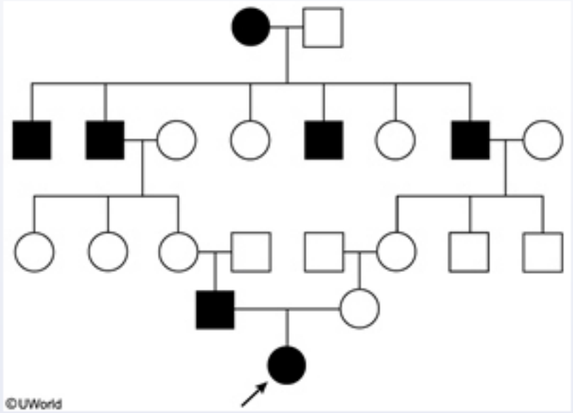
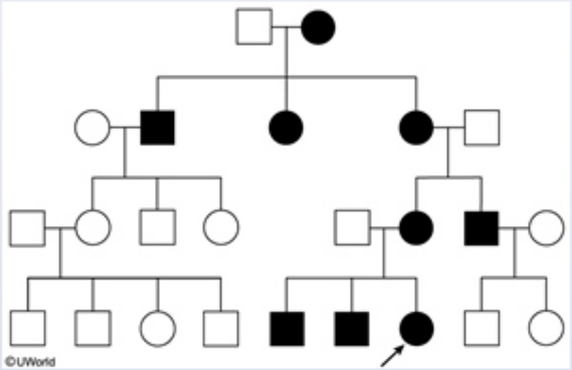


D. (3%)



✓ E. (84%)



Omitted
Correct answer

84%
Answered correctly

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03/04/2020
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Explanation

This patient most likely has a form of **mitochondrial myopathy**. Without properly functioning mitochondria, cells are unable to use oxidative phosphorylation to efficiently produce adequate levels of ATP. Organ systems such as the brain and skeletal muscle will be affected first due to their high metabolic demand relative to other tissues. Affected patients often present with myopathy (eg, **muscle weakness**, myalgia), lactic acidosis due to impaired aerobic glycolysis, and **nervous system dysfunction** (eg, neuropathy, seizures). Muscle biopsy classically shows **ragged red fibers**.

Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with no paternal contribution (**maternal inheritance**). Only affected females transmit abnormal mitochondria to offspring; transmission never occurs through males (even if they are affected).

(Choice A) Autosomal dominant disorders affect 50% of all children (males and females) born to one affected parent. The disease will appear in consecutive generations, and father-to-son transmission can occur.

(Choice B) Autosomal recessive conditions affect about 25% of all children (males and females) with two carrier parents. Offspring of a single affected parent will be carriers for the disorder. As a result, the disease can skip generations, but consanguineous families will show increased incidence.

(Choice C) In X-linked dominant disorders, all female children of affected males will have the condition, but both female and male children of an affected female have a 50% chance of being affected. There is no father-to-son transmission.

(Choice D) In X-linked recessive conditions, male offspring of a carrier female have a 50% chance of being affected, whereas female offspring have a 50% chance of being carriers. Female children of an affected father are obligate carriers. The disease can skip generations, and there is no father-to-son transmission.

Educational objective:
Mitochondrial dysfunction frequently presents with myopathy, nervous system dysfunction, lactic acidosis, and ragged red fibers on muscle biopsy. Mitochondrial myopathies due to mtDNA mutations are inherited solely in a maternal fashion (ie, maternal inheritance). Therefore, transmission occurs only through affected females and never through males.

Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with no paternal contribution (**maternal inheritance**). Only affected females transmit abnormal mitochondria to offspring; transmission never occurs through males (even if they are affected).

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(Choice D) In X-linked recessive conditions, male offspring of a carrier female have a 50% chance of being affected, whereas female offspring have a 50% chance of being carriers. Female children of an affected father are obligate carriers. The disease can skip generations, and there is no father-to-son transmission.

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Mitochondrial dysfunction frequently presents with myopathy, nervous system dysfunction, lactic acidosis, and ragged red fibers on muscle biopsy. Mitochondrial myopathies due to mtDNA mutations are inherited solely in a maternal fashion (ie, maternal inheritance). Therefore, transmission occurs only through affected females and never through males.

References

- Maternal inheritance of mitochondrial DNA by diverse mechanisms to eliminate paternal mitochondrial DNA.

Genetics	General Principles	Mitochondrial disorders
Subject	System	Topic

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Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with

Exhibit Display

X-linked dominant inheritance

Affected father

Father \ Mother	X	X
Xd	XXd	XXd
Y	XY	XY

All daughters are affected

All sons are normal

Affected mother

Father \ Mother	X	Xd
X	XX	XXd
Y	XY	XdY

All sons & daughters have 50% chance of being affected

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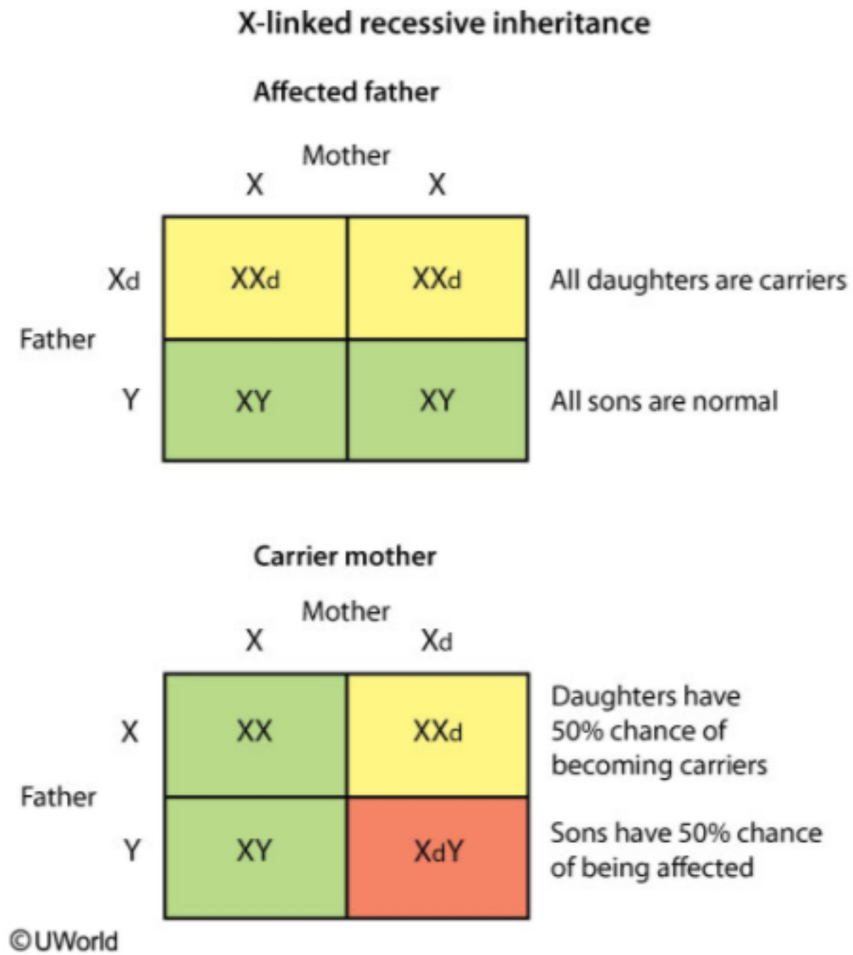
Mitochondria are unique organelles because they contain their own DNA, known as **mtDNA**. Offspring inherit mtDNA in a maternal fashion with

Exhibit Display



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A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

A. Dominant negative mutation
B. Genetic linkage
C. Incomplete penetrance
D. Locus heterogeneity
E. Pleiotropy
F. Polyploidy
G. Segregation

Submit

A 10-year-old boy is brought to the emergency department for new swelling in his right leg. He has a history of lens dislocation and intellectual disability. Physical examination demonstrates moderate, pitting edema from his right calf to his right thigh and a normal left lower extremity. In addition, the patient has a caved-in appearing chest wall. He has no family members with similar conditions. Ultrasound reveals a deep venous thrombosis in his right femoral vein. Further genetic testing reveals a single missense mutation in the gene coding for cystathionine beta-synthase enzyme. Which of the following is the most likely explanation for this patient's genetic defect affecting multiple tissues?

- A. Dominant negative mutation (5%)
- B. Genetic linkage (3%)
- C. Incomplete penetrance (2%)
- D. Locus heterogeneity (10%)
- ✓ E. Pleiotropy (74%)
- F. Polyploidy (3%)
- G. Segregation (0%)

Omitted
Correct answer
E

74%
Answered correctly

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Time Spent

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Last Updated

Explanation

This patient presenting with skeletal abnormalities, lens dislocation, intellectual deficits, vascular thromboses, and a genetic defect in the cystathionine beta-synthase enzyme likely has homocystinuria. The occurrence of **multiple**, seemingly unrelated **phenotypic manifestations**

This patient presenting with skeletal abnormalities, lens dislocation, intellectual deficits, vascular thromboses, and a genetic defect in the cystathionine beta-synthase enzyme likely has homocystinuria. The occurrence of **multiple**, seemingly unrelated **phenotypic manifestations**, often in different organ systems, as a result of a **single genetic defect** is termed **pleiotropy**. Most syndromic genetic illnesses including homocystinuria exhibit pleiotropy.

(Choice A) Dominant negative mutations occur when an abnormal gene negatively affects the product of the wild-type gene in the same cell. For example, certain oncogene *p53* mutations can lead to translation of a protein product that prevents wild-type *p53* from binding to the promoter of its target genes.

(Choice B) Genetic linkage describes the tendency of alleles located near one another on the same chromosome to be inherited jointly.

(Choice C) Penetrance refers to the proportion of individuals with a given genotype that express the associated phenotype. In incomplete penetrance, less than 100% of individuals with a given genotype express its associated phenotype.

(Choice D) Locus heterogeneity refers to the ability of one disease or trait to be caused by mutations in multiple different genes. An example is familial hypercholesteremia, which can be caused by different mutations affecting cholesterol metabolism genes (eg, LDL receptor, apo B-100).

(Choice F) Polyploidy occurs when more than 2 complete sets of homologous chromosomes exist within an organism or cell. In a partial hydatidiform mole, for example, there are cells of nonstandard ploidy (typically 69,XXX; 69,XXY; or 69,XYY). The chromosomes in this case are derived from 1 haploid maternal set and 2 haploid paternal sets of chromosomes.

(Choice G) The law of segregation (Mendel's first law) describes the phenomenon whereby gametogenesis within the parent organism results in the separation of paired alleles so that each offspring inherits only half of each parent's genetic composition.

Educational objective:
Pleiotropy describes instances where multiple phenotypic manifestations result from a single genetic mutation. Most syndromic genetic illnesses exhibit pleiotropy.

References

- Pleiotropy in complex traits: challenges and strategies.

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Exhibit Display

Features of homocystinuria

Pathogenesis

- Most commonly due to an autosomal recessive mutation causing cystathionine synthase deficiency

Clinical findings

- Optic lens dislocation
- Intellectual disability
- Marfanoid habitus (eg, elongated limbs & arachnodactyly)
- Thromboembolic complications

Diagnosis

- ↑ plasma and urinary homocystine levels

Treatment

- Pyridoxine (vitamin B6) administration
- Dietary methionine restriction & cysteine supplementation

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A 5-year-old boy is being evaluated for progressive muscle weakness that has resulted in numerous recent falls. There is no family history of muscle disorders. Physical examination reveals bilateral calf enlargement. When the patient is asked to stand, he uses his hands and arms to help push himself to an upright position. Serum creatine kinase is 12,600 U/L (normal: 30-170 U/L). Molecular tests reveal a large muscle protein that is defective due to the loss of 508 amino acid residues. Genetic analysis reveals a single base substitution within exon 48 of the gene encoding this muscle protein. This patient's gene mutation has most likely resulted in which of the following mRNA codon changes?

A. CUU → AUU

B. UAA → UAG

C. UAC → CAC

D. UCA → UGA

E. UUU → UUC

Submit

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- A. CUU → AUU (3%)
- B. UAA → UAG (19%)
- C. UAC → CAC (5%)
- ✓ D. UCA → UGA (69%)
- E. UUU → UUC (1%)

Omitted
Correct answer
D

69%
Answered correctly

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Explanation

Types of DNA mutations	
Silent	Base substitution codes for same amino acid

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Explanation

Types of DNA mutations	
Silent	Base substitution codes for same amino acid
Missense	Base substitution codes for different amino acid
Conservative	Base substitution codes for different amino acid with similar chemical structure
Nonsense	Base substitution introduces premature stop codon
Nonstop	Base substitution within stop codon results in continued translation
Splice site	Mutation at splice site alters intron removal from pre-mRNA
Frameshift	Deletion/insertion of bases causes downstream misreading

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This young boy with progressive proximal muscle weakness, calf pseudohypertrophy, Gowers sign, and elevated creatine kinase likely has **Duchenne muscular dystrophy**, an X-linked recessive disorder caused by mutations in the dystrophin gene. Although Duchenne muscular dystrophy is most commonly caused by **deletions** resulting in frameshift mutations, **nonsense mutations** may also occur, leading to the formation of a truncated dystrophin protein.

After messenger RNA (mRNA) is produced from DNA and posttranscriptionally modified, it is transported to the cytoplasm for translation into

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After messenger RNA (mRNA) is produced from DNA and posttranscriptionally modified, it is transported to the cytoplasm for translation into protein. mRNA is composed of groups of 3 sequential nucleotide bases known as codons. These nucleotide triplets code for specific amino acids and signal for the initiation (eg, start codon [AUG]) or termination of translation (eg, **stop codons** [**UAA, UAG, UGA**]). In this case, a single base substitution from UCA (serine) to UGA has introduced a **premature** stop codon in the middle of the protein sequence (nonsense mutation), resulting in early termination of protein synthesis.

Dystrophin normally links with actin fibers and provides mechanical reinforcement to glycoprotein complexes in the plasma membrane of skeletal muscle cells. Consequently, dystrophin dysfunction leads to increased breakdown of the sarcolemma, muscle fiber degeneration, and the clinical findings described above.

(Choices A and C) Changing CUU (leucine) to AUU (isoleucine) or UAC (tyrosine) to CAC (histidine) would result in an amino acid substitution at one position (missense mutation). The function of this protein may be altered depending on a variety of factors, but the ultimate size of the protein will remain the same. Missense mutations that result in the substitution of a new amino acid with similar chemical properties are called conservative mutations.

(Choice B) Changing UAA to UAG would not affect protein structure or function because both of these sequences are stop codons. Stop codons are normally located at the end of the translated region of mRNA.

(Choice E) Changing UUU to UUC would not affect the protein as both sequences code for phenylalanine. Point mutations that do not change the amino acid sequence of a protein are called silent mutations.

Educational objective:
Duchenne muscular dystrophy presents with progressive proximal muscle weakness in young boys due to increased muscle fiber degeneration. It is caused by frameshift mutations (most common) or nonsense mutations in the dystrophin gene that lead to the formation of a truncated,

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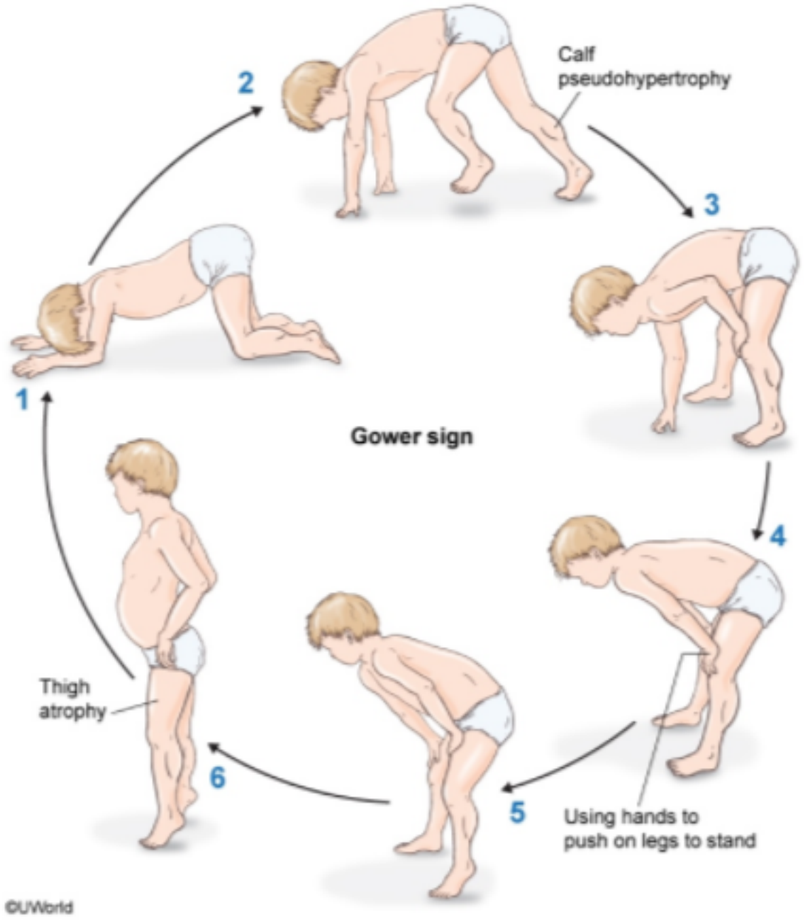

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Educational objective:
Duchenne muscular dystrophy presents with progressive proximal muscle weakness in young boys due to increased muscle fiber degeneration. It is caused by frameshift mutations (most common) or nonsense mutations in the dystrophin gene that lead to the formation of a truncated, defective protein. Nonsense mutations introduce premature stop codons (eg, UAA, UAG, UGA) in the coding sequence of mRNA.

References

- Mutation spectrum of the dystrophin gene in 442 Duchenne/Becker muscular dystrophy cases from one Japanese referral center.

Genetics	General Principles	Mutations
Subject	System	Topic

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A 50-year-old previously healthy man is evaluated for progressive fatigue, weakness, and recurrent gingival bleeding. Laboratory studies reveal normocytic normochromic anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. Induction chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is planned. Molecular typing of human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, and -DR is performed. The patient's biological sister, with whom he shares both parents, is eligible for stem cell donation and undergoes HLA typing. Which of the following is the most likely probability that the sibling will be an identical HLA match with this patient?

A. 0
B. 1/16
C. 1/8
D. 1/4
E. 1/2

Submit

A 50-year-old previously healthy man is evaluated for progressive fatigue, weakness, and recurrent gingival bleeding. Laboratory studies reveal normocytic normochromic anemia, thrombocytopenia, and leukocytosis with circulating myeloblasts. Bone marrow biopsy establishes a diagnosis of acute myeloid leukemia. Induction chemotherapy followed by allogeneic hematopoietic cell transplantation (HCT) is planned. Molecular typing of human leukocyte antigen (HLA) -A, -B, -C, -DP, -DQ, and -DR is performed. The patient's biological sister, with whom he shares both parents, is eligible for stem cell donation and undergoes HLA typing. Which of the following is the most likely probability that the sibling will be an identical HLA match with this patient?

- A. 0 (7%)
- B. 1/16 (15%)
- C. 1/8 (10%)
- ✓ D. 1/4 (55%)
- E. 1/2 (10%)

Omitted
Correct answer
D

55%
Answered correctly

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Explanation

HLA inheritance

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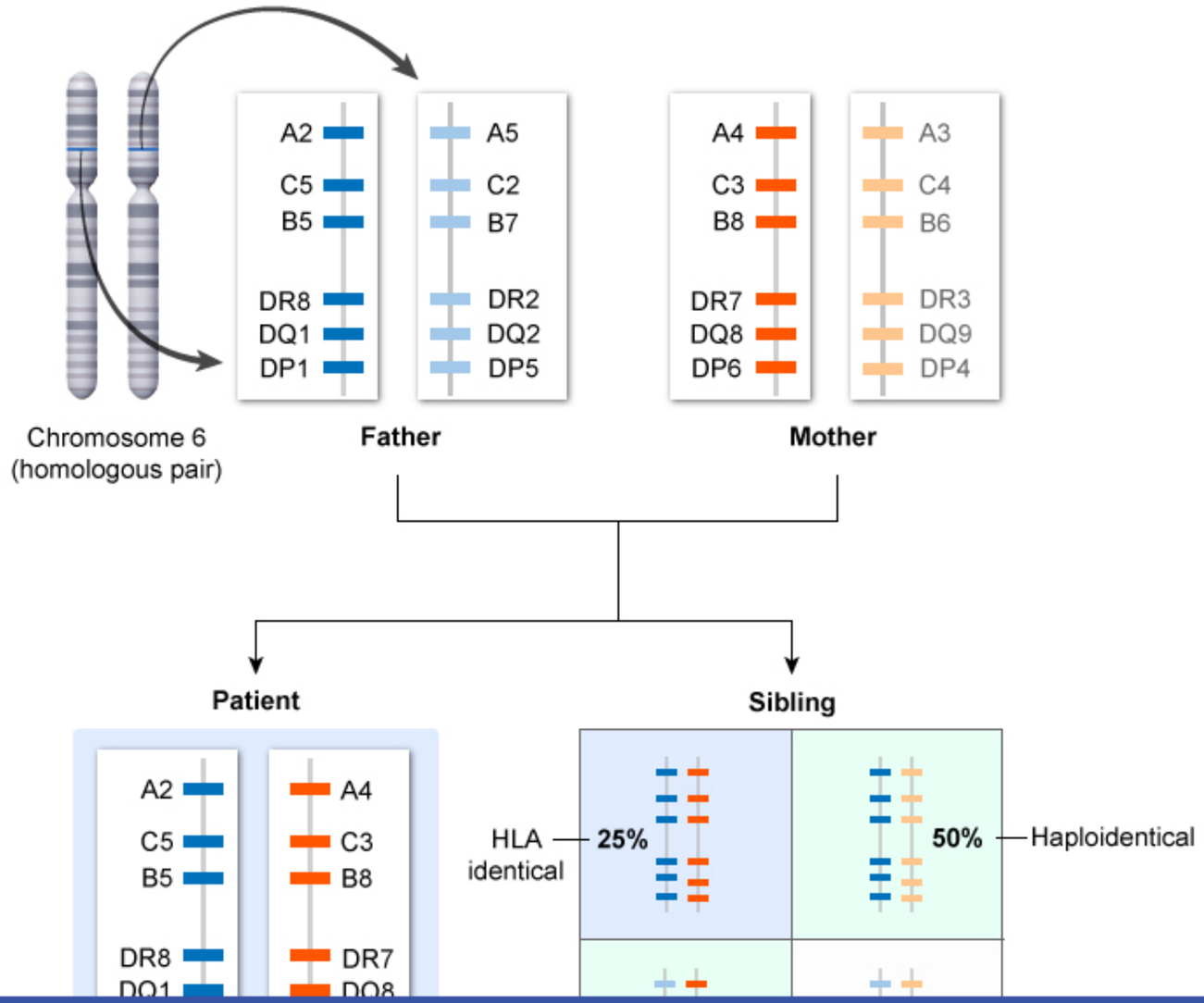
HLA inheritance



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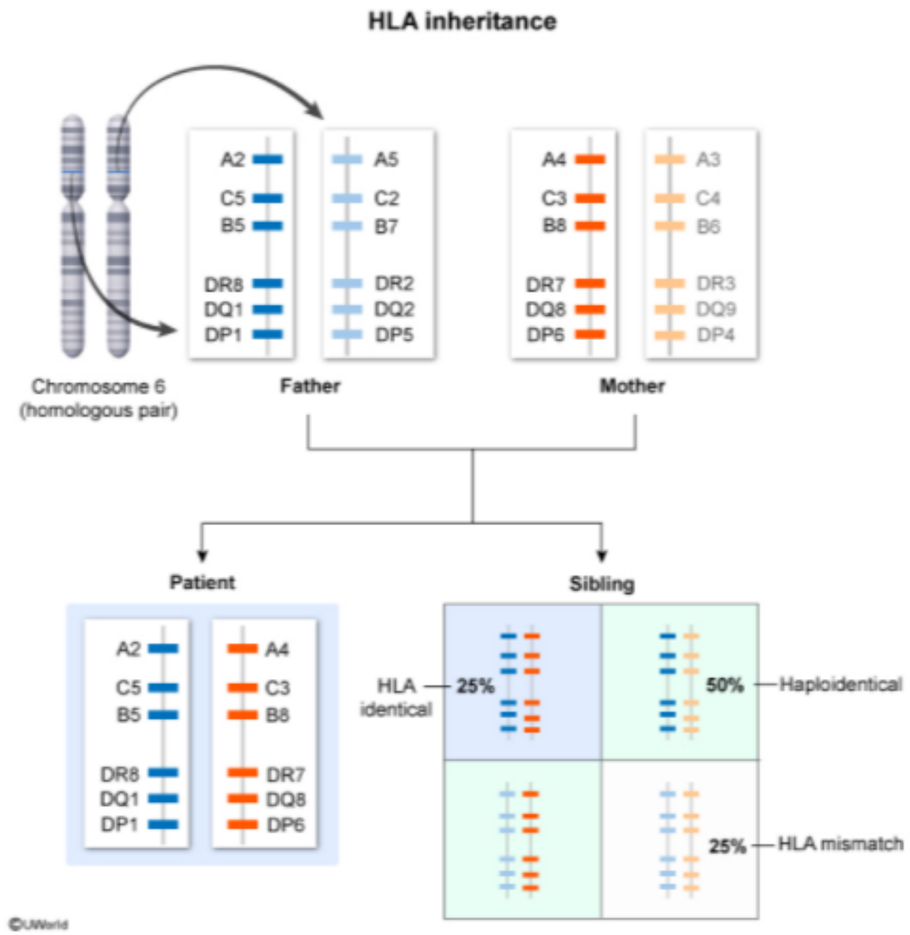

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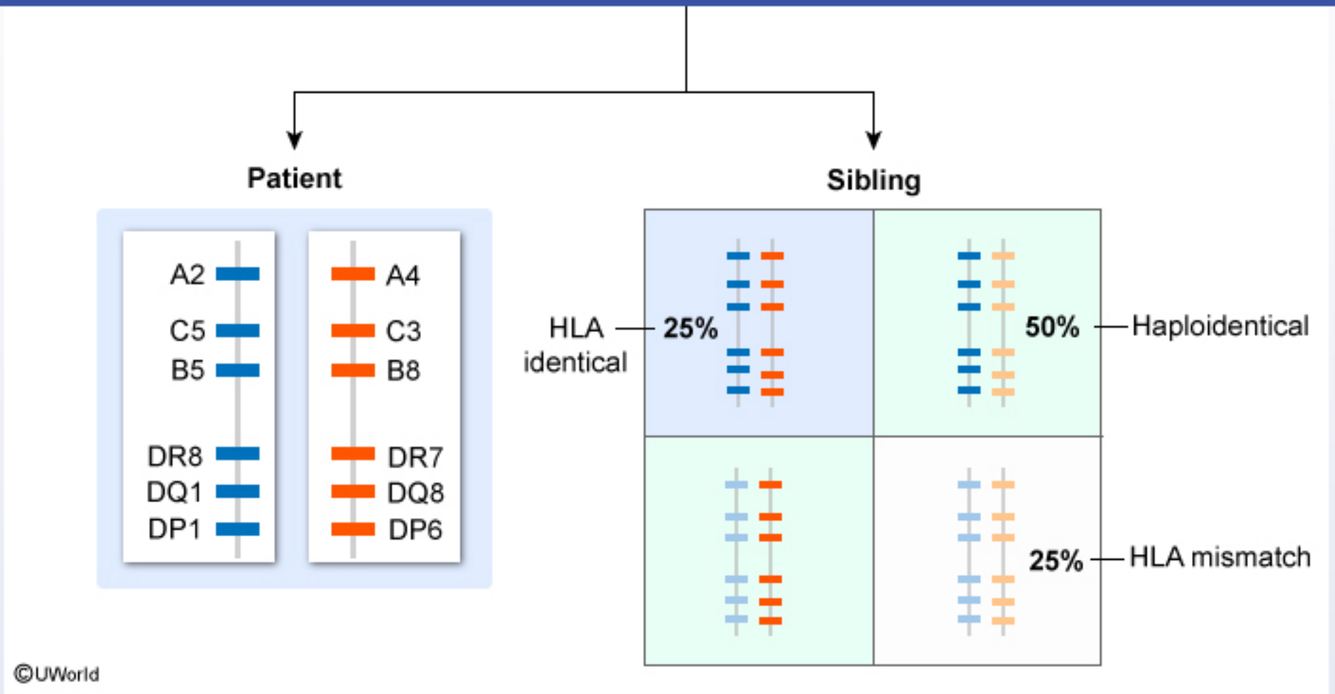

The human leukocyte antigen **(HLA)** genes encode major histocompatibility complex **(MHC)** molecules that are expressed on the cell surface and are key to recognition of cells as **self or non-self** by the immune system. These include major class I genes (eg, HLA-A, HLA-B, HLA-C) and class II genes (eg, HLA-DP, HLA-DQ, HLA-DR), along with other minor HLA genes.

Although there are thousands of HLA alleles in the human population with millions of potential combinations, the HLA genes are **clustered** within a short region of a single chromosome. This results in a **low** rate of **crossover**, allowing the HLA gene cluster to be treated as an **HLA haplotype** (a series of **linked genes** on the same chromosome). Each child inherits 2 HLA haplotypes, one from the mother and one from the father. Therefore, the probabilities that a given sibling will share some or all of the same HLA genes are as follows:

- **1/4** chance of inheriting all the same HLA genes (ie, **identical HLA match**).
- 1/2 chance of inheriting half of the same HLA genes (ie, haploidentical HLA match) **(Choice E)**.
- 1/4 chance of inheriting none of the same HLA genes (ie, HLA mismatch).

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- 1/2 chance of inheriting half of the same HLA genes (ie, haploidentical HLA match) **(Choice E)**.
- 1/4 chance of inheriting none of the same HLA genes (ie, HLA mismatch).

Molecular typing of HLA antigens is performed prior to transplants (eg, allogeneic stem cell transplant) to evaluate potential donors for mismatch in HLA alleles (eg, HLA-DR8 versus HLA-DR3), which is associated with higher rates of posttransplant complications (eg, graft versus host disease, graft failure). An **HLA-identical sibling donor** would drastically reduce the likelihood of serious complications and increase the likelihood of a **successful transplant**.

Educational objective:
The human leukocyte antigen (HLA) genes encode major histocompatibility complex (MHC) molecules that are key to activation of the immune system in response to foreign (non-self) antigens. All the HLA genes are clustered together, meaning that there is a low rate of crossover and that offspring essentially inherit 2 HLA haplotypes, one from each parent. Therefore, the probability that a sibling would be an identical HLA match is 1/4.

Genetics	General Principles	Genetic inheritance
Subject	System	Topic

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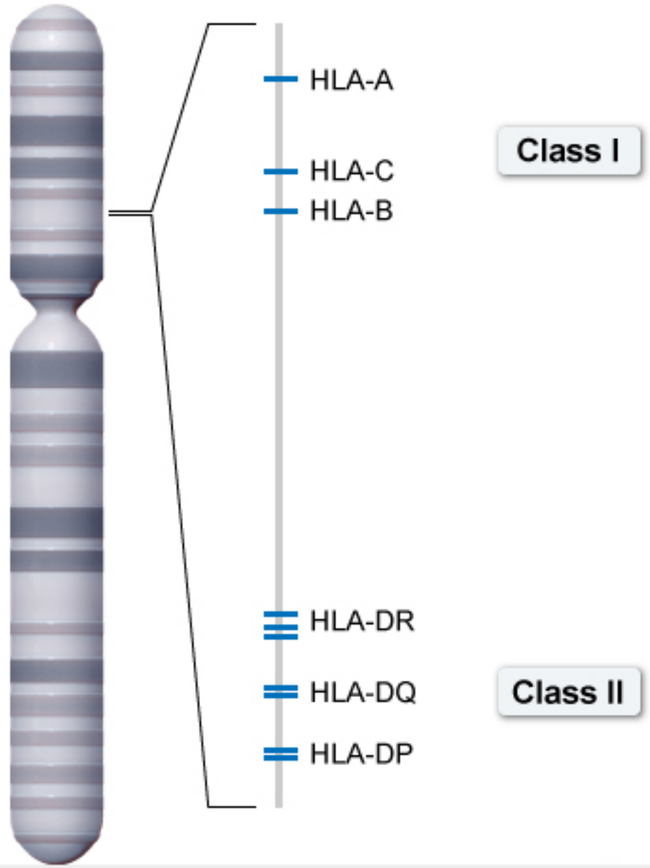
HLA genes (chromosome 6)



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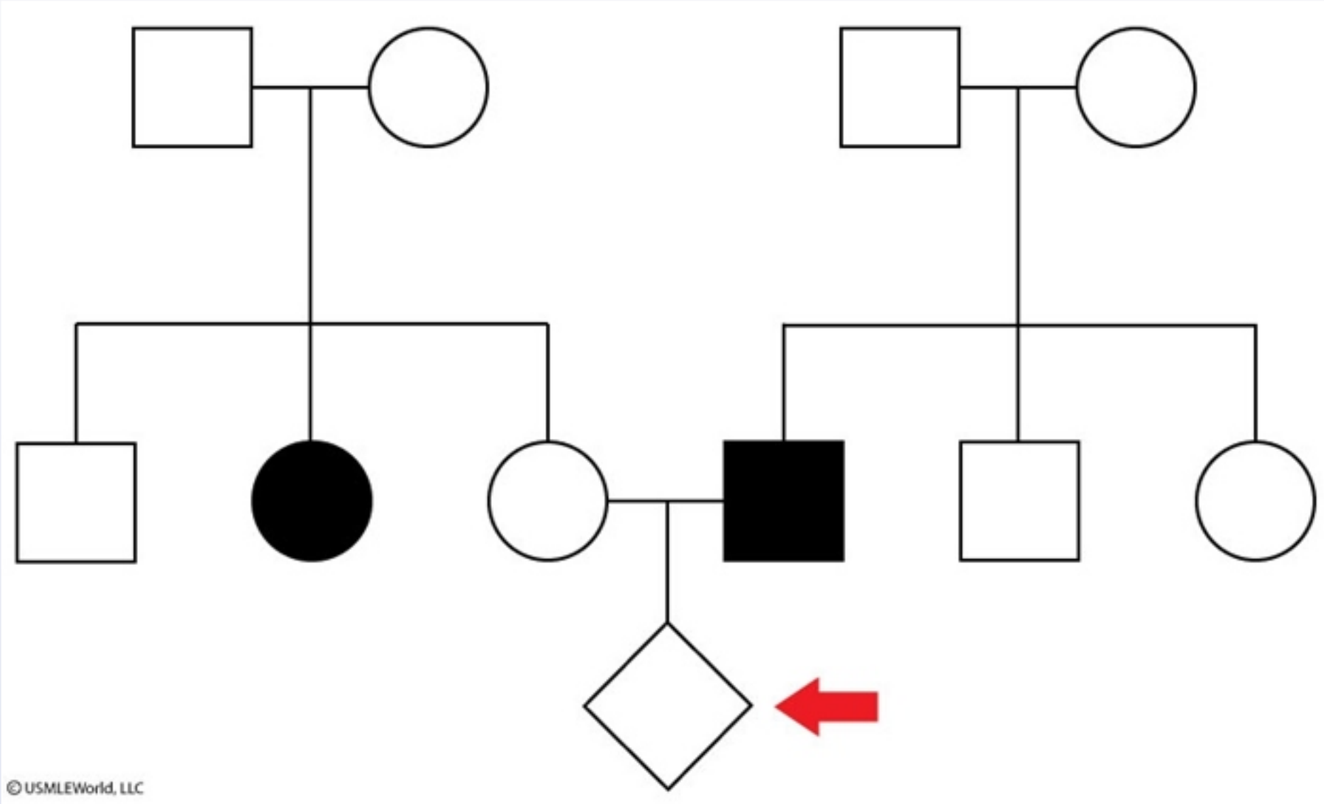
A young couple has undergone a successful in vitro fertilization procedure. The father has cystic fibrosis and the mother has a sister with cystic fibrosis. The father as well as the mother's sister are both known to have ΔF508 mutations, but the mother's carrier status is unknown. Before making the decision to conceive, the couple underwent extensive genetic counseling regarding the potential risks of having a child with cystic fibrosis. The family pedigree is diagrammed below with the unborn child marked by the red arrow.



What is the probability that the unborn child will have cystic fibrosis?

A. 1/16

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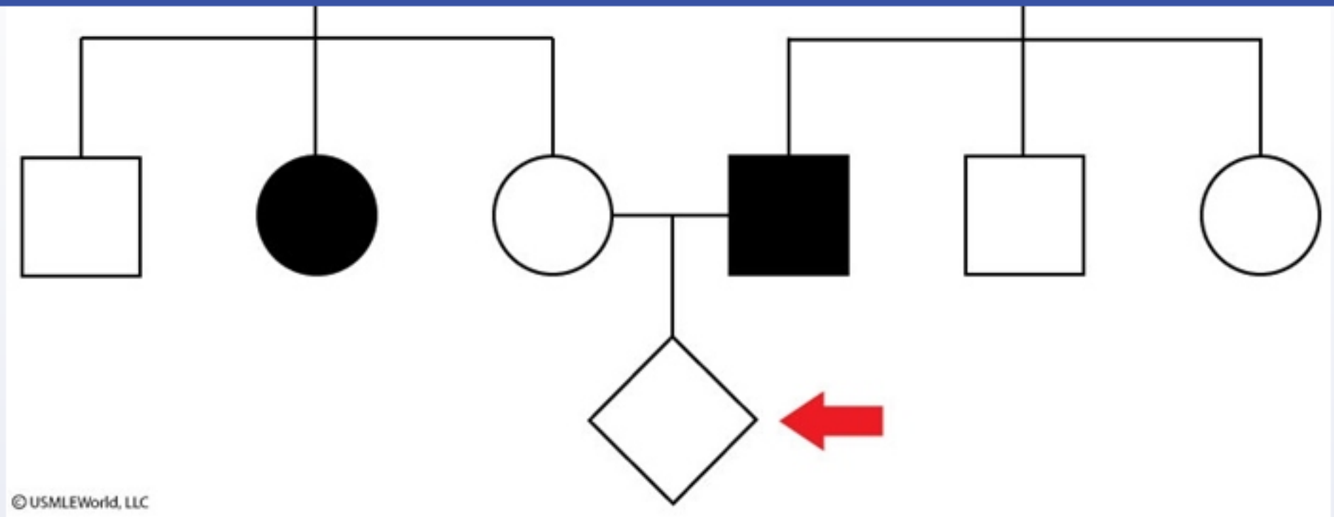

What is the probability that the unborn child will have cystic fibrosis?

- A. 1/16
- B. 1/8
- C. 1/4
- D. 1/3
- E. 2/3
- F. 3/4

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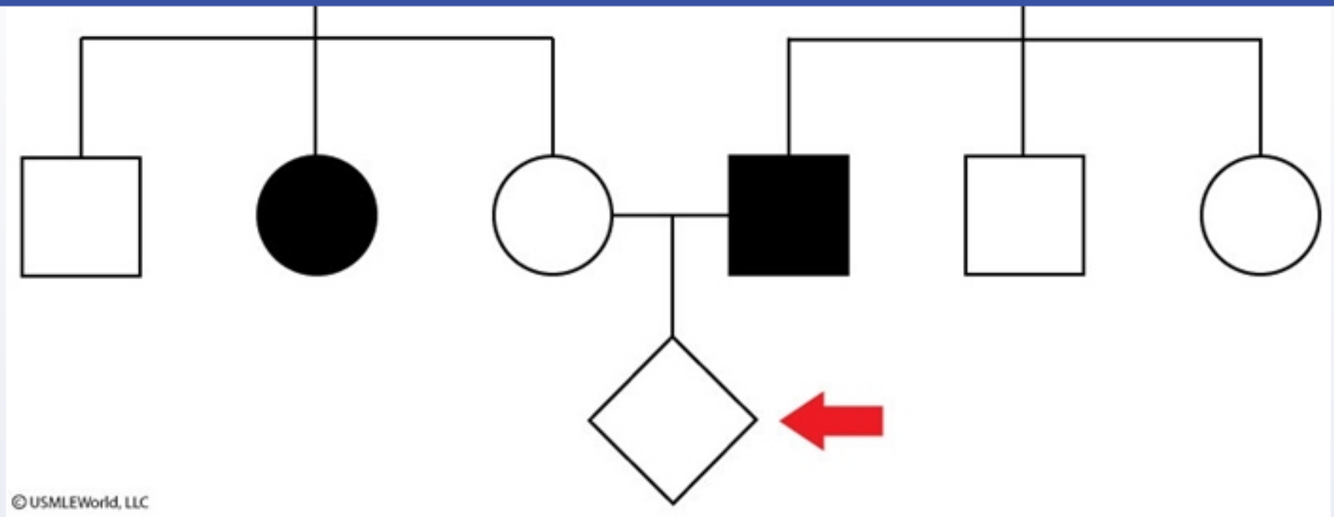

What is the probability that the unborn child will have cystic fibrosis?

- A. 1/16 (3%)
- B. 1/8 (12%)
- C. 1/4 (31%)
- ✓ D. 1/3 (35%)
- E. 2/3 (11%)
- F. 3/4 (5%)

Omitted
Correct answer

35%
Answered correctly

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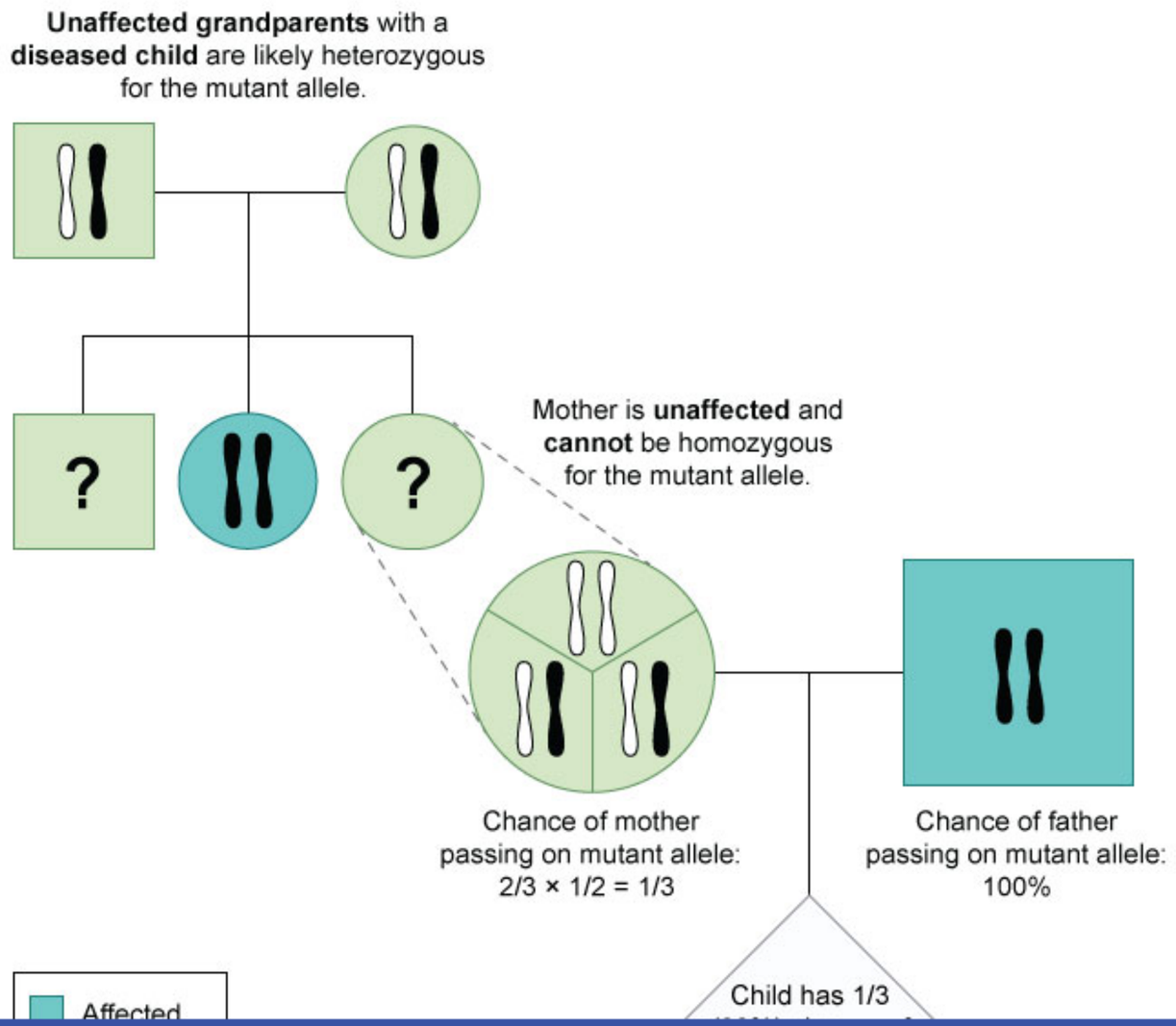
Probability of the child having cystic fibrosis



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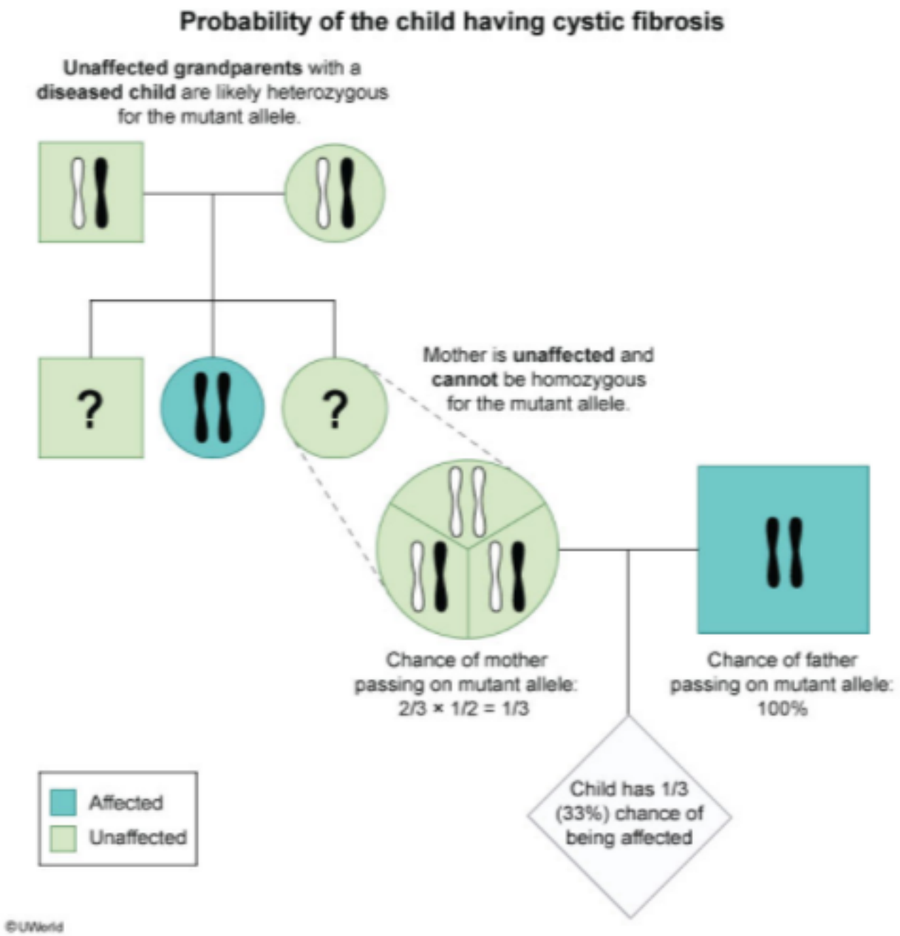

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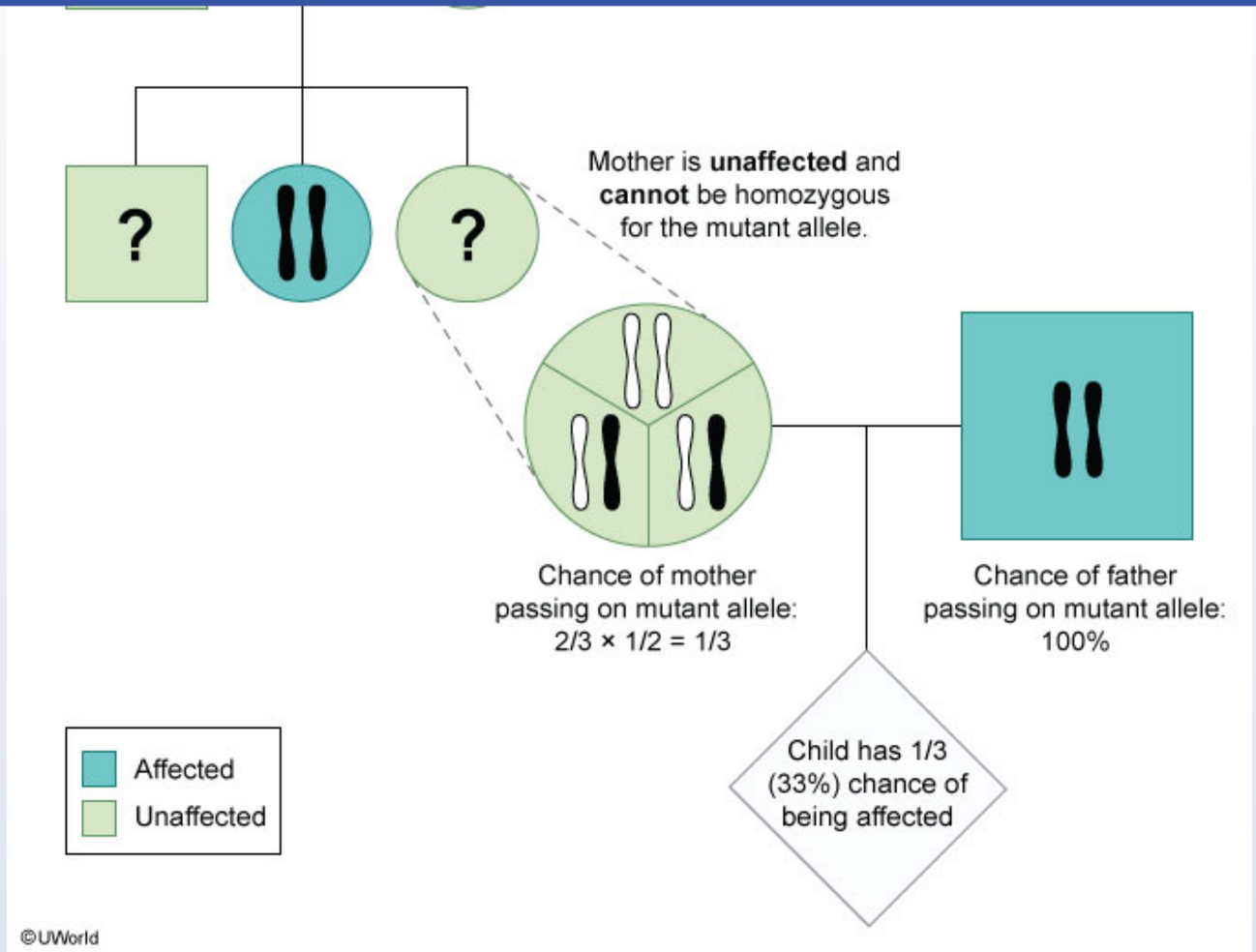

Cystic fibrosis (CF) results from an **autosomal recessive** defect in the CF transmembrane conductance regulator (*CFTR*) gene. Although most men with CF are infertile due to congenital absence of the vas deferens, they are **not sterile** and can have children via assisted reproductive technology.

Calculating the probability that the unborn child will have CF can be done by analyzing the above pedigree as follows:

Cystic fibrosis (CF) results from an **autosomal recessive** defect in the CF transmembrane conductance regulator (*CFTR*) gene. Although most men with CF are infertile due to congenital absence of the vas deferens, they are **not sterile** and can have children via assisted reproductive technology.

Calculating the probability that the unborn child will have CF can be done by analyzing the above pedigree as follows:

1. Because the **father** is homozygous for the mutant *CFTR* allele, he will **always** transmit the mutant allele to his offspring.
2. Because the **mother** has an affected sibling and neither of her parents is affected, she most likely had 2 heterozygous carrier parents. Therefore, the mother's 4 possible genotypes are: homozygous for the normal allele, heterozygous with her mother's mutant allele, heterozygous with her father's mutant allele, and homozygous for the mutant allele. However, the mother does **not have CF** and therefore is **not homozygous for the mutant allele**. This leaves 3 possible genotypes for the mother. Two of the 3 remaining genotypes result in her being a **carrier** for the mutant *CFTR* allele, while the last one results in her being homozygous normal. Therefore, the mother's probability of being a carrier equals **2/3**.
3. If the mother is a carrier (2/3 chance), the probability that she will transmit the mutant allele to the child is 1 in 2. As a result, the probability that the child will inherit a mutant allele from the mother (and therefore have CF as the father will always contribute a mutant allele) is: 2/3 x 1/2 = **1/3**.

Educational objective:
The probability that an autosomal recessive disease will be transmitted to a child can be calculated based on the maternal and paternal pedigrees. An unaffected individual (with unaffected parents) who has a sibling affected by an autosomal recessive condition has a 2/3 chance of being a carrier for that condition.

References

- Genetic counseling issues in cystic fibrosis.
- Cystic fibrosis and fertility.

Genetics General Principles Autosomal recessive inheritance

technology.

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The probability that an autosomal recessive disease will be transmitted to a child can be calculated based on the maternal and paternal pedigrees. An unaffected individual (with unaffected parents) who has a sibling affected by an autosomal recessive condition has a 2/3 chance of being a carrier for that condition.

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- Cystic fibrosis and fertility.

Genetics	General Principles	Autosomal recessive inheritance
Subject	System	Topic

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In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are chemically removed to isolate nucleic acids. The cellular extract containing the purified nucleic acids is incubated along with short sequences of repeated deoxythymidine residues fixed to latex beads. The solution is washed several times to remove unbound molecules. Which of the following types of nucleic acid is most likely to bind the strongest to the latex beads in this experiment?

A. Aminoacyl-tRNA
B. Mature mRNA
C. Promoter regions of DNA
D. Ribosomal RNA
E. Splice sites of pre-mRNA
F. Telomere regions of chromosomes

Submit

In an experiment, cultured fibroblasts are mechanically lysed, and the membrane lipids and cellular proteins are chemically removed to isolate nucleic acids. The cellular extract containing the purified nucleic acids is incubated along with short sequences of repeated deoxythymidine residues fixed to latex beads. The solution is washed several times to remove unbound molecules. Which of the following types of nucleic acid is most likely to bind the strongest to the latex beads in this experiment?

- A. Aminoacyl-tRNA (13%)
- ✓ B. Mature mRNA (28%)
- C. Promoter regions of DNA (28%)
- D. Ribosomal RNA (7%)
- E. Splice sites of pre-mRNA (5%)
- F. Telomere regions of chromosomes (15%)

Omitted
Correct answer
B

28%
Answered correctly

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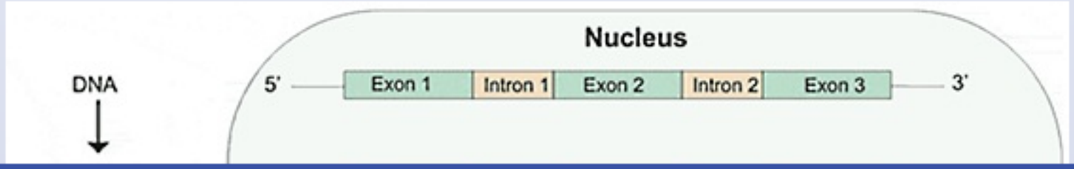
Explanation



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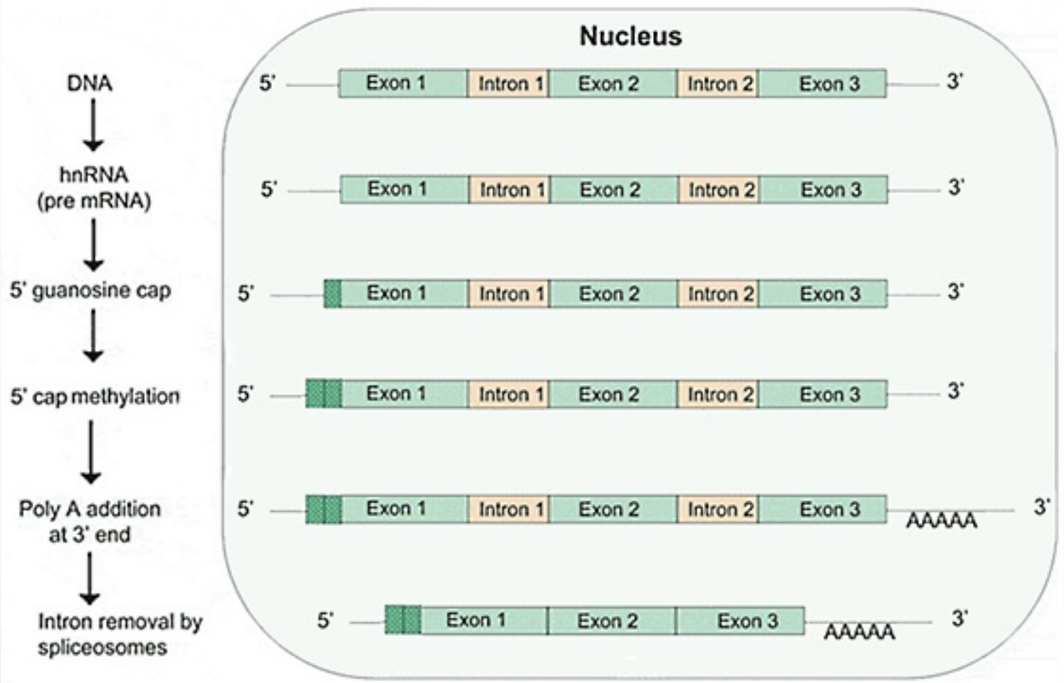

In the experiment described above, the poly-A tail on mature mRNA is most likely to bind the latex beads because the adenine residues in this tail would form complementary base pairs with the repeated deoxythymine residues fixed to the beads.

Mature mRNA refers to mRNA that has been processed and is ready for nuclear export and translation into protein. mRNA processing (**post-transcriptional modification**) involves the following steps:

1. 5' capping: A 7-methyl-guanosine cap is added to the 5' end of the mRNA.
2. Polyadenylation: A **poly-A tail** (chain of adenine residues) is added to most eukaryotic mRNA molecules by poly-A polymerase. Poly-A tails are not transcribed from the DNA template. Instead, a **consensus sequence (AAUAAA)** located near the **3'** end of the RNA molecule directs the addition of the poly-A tail. This tail protects the mRNA from degradation within the cytoplasm after it exits the nucleus.
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3. Splicing: The initial mRNA transcript (pre-mRNA) contains sequences from coding and noncoding regions of DNA, known as exons and introns, respectively. Spliceosomes (complexes of small nuclear ribonucleoproteins [snRNPs] and other proteins) remove introns containing GU at the 5' splice site and AG at the 3' splice site **(Choice E)**.

(Choice A) Aminoacyl-tRNA is tRNA charged with its amino acid. The cloverleaf structure of tRNA consists of a 3' CCA tail (amino acid binding site); a T loop abundant in ribothymidine, pseudouridine, and cytidine residues; a D loop rich in dihydrouridine residues; and an anticodon loop.

(Choice C) DNA promoter regions help initiate transcription by binding transcription factors and RNA polymerase II. Promoter regions contain consensus sequences that are typically AT-rich (eg, TATA and CAAT boxes) or GC-rich (eg, GC box).

(Choice D) Ribosomal RNA (rRNA) is a component of the ribosome that catalyzes peptide bond formation during translation.

(Choice F) Telomeres are located at the ends of chromosomes and contain TTAGGG repeats, which are added by the enzyme telomerase (RNA-dependent DNA polymerase). Critical shortening in telomere length is thought to signal programmed cell death.

Educational objective:
The poly-A tail is not transcribed from DNA; instead, it is added as a post-transcriptional modification downstream of the consensus sequence (AAUAAA) located near the 3' end of the mRNA molecule. This tail protects mRNA from degradation within the cytoplasm after it exits the nucleus.

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References

- Ending the message: poly(A) signals then and now.

Genetics	General Principles	Poly a tail
Subject	System	Topic

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A 4-year-old boy is brought to the physician for fatigue and persistent bone pain. Physical examination shows diffuse lymphadenopathy and multiple purpura over his arms and legs. Laboratory analysis reveals anemia and thrombocytopenia, and a peripheral blood smear shows lymphoblasts. After further workup, he is diagnosed with acute lymphoblastic leukemia and started on a chemotherapy regimen that includes doxorubicin. This agent intercalates between DNA base pairs and inhibits DNA replication, a process that normally occurs at sites known as replication forks. As the replication forks move across the DNA molecule, 2 distinct daughter strands are formed. Which of the following is unique to the daughter strand that is synthesized in the opposite direction of the growing replication fork?

A. Synthesis of multiple, short DNA fragments

B. 5'→3' exonuclease activity of DNA polymerase

C. 3'→5' exonuclease activity of DNA polymerase

D. 3'→5' polymerase activity of DNA polymerase

E. RNA primer synthesis before DNA strand synthesis

Submit

A 4-year-old boy is brought to the physician for fatigue and persistent bone pain. Physical examination shows diffuse lymphadenopathy and multiple purpura over his arms and legs. Laboratory analysis reveals anemia and thrombocytopenia, and a peripheral blood smear shows lymphoblasts. After further workup, he is diagnosed with acute lymphoblastic leukemia and started on a chemotherapy regimen that includes doxorubicin. This agent intercalates between DNA base pairs and inhibits DNA replication, a process that normally occurs at sites known as replication forks. As the replication forks move across the DNA molecule, 2 distinct daughter strands are formed. Which of the following is unique to the daughter strand that is synthesized in the opposite direction of the growing replication fork?

- ✓ A. Synthesis of multiple, short DNA fragments (75%)
- B. 5'→3' exonuclease activity of DNA polymerase (6%)
- C. 3'→5' exonuclease activity of DNA polymerase (8%)
- D. 3'→5' polymerase activity of DNA polymerase (3%)
- E. RNA primer synthesis before DNA strand synthesis (5%)

Omitted
Correct answer
A

75%
Answered correctly

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Explanation

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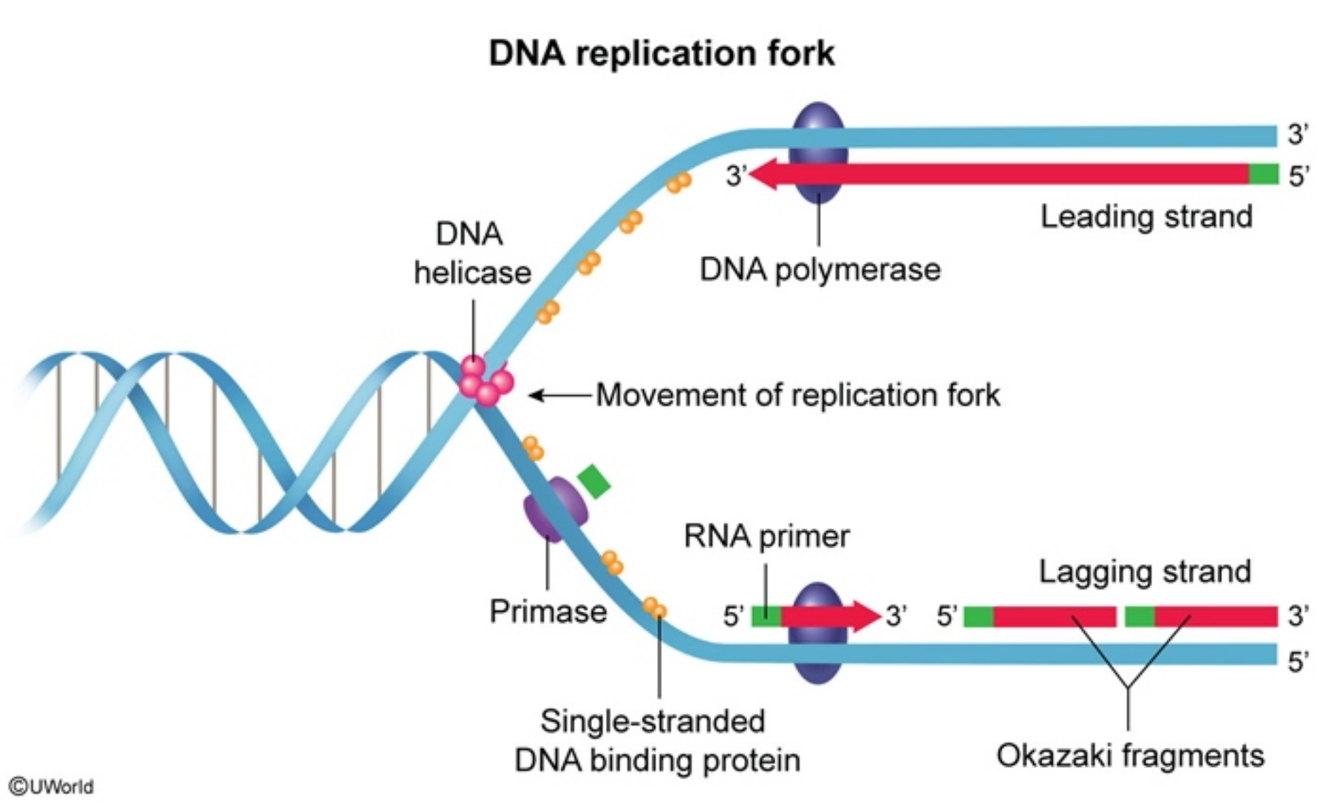

DNA replication begins at **multiple sites** within eukaryotic chromosomes called origins of replication. At these sites, the parent DNA double helix is separated and unwound in a process facilitated by the helicase enzyme and single-stranded DNA-binding proteins. The locations where unwound DNA meets the double helix are known as replication forks. Replication forks travel bidirectionally away from the origin of replication as DNA polymerase synthesizes complementary daughter DNA strands.

Synthesis of the daughter strands occurs simultaneously from both parent strands. Because **DNA synthesis can occur only in the 5'→3' direction**, one daughter strand is synthesized **continuously** toward the replication fork (**leading strand**). However, the other strand must be synthesized **discontinuously** in a direction away from the replication fork (**lagging strand**), with more and more segments being added as the

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(Choice B) 5'→3' exonuclease activity is needed during the synthesis of both daughter strands to remove RNA primers (although there are many more primers on the lagging strand, primers must also be removed when joining leading strands from seperate origins of replication). In addition, 5'→3' and exonuclease activity is necessary to correct DNA replication errors that occur on both strands.

(Choice C) DNA polymerases have 3'→5' exonuclease activity (proofreading function) that allows them to reverse direction and remove incorrectly placed bases. This process occurs on both newly formed daughter strands to help reduce replication errors.

(Choice D) DNA polymerases do not have 3'→5' polymerase activity; all known polymerases synthesize in the 5'→3' direction.

(Choice E) Before DNA polymerase can initiate DNA synthesis, RNA primers must first be synthesized by the enzyme primase (DNA-dependent RNA polymerase). This process is necessary for synthesis of both daughter strands (even though it occurs much more frequently on the lagging strand).

Educational objective:
DNA synthesis can occur only in the 5'→3' direction. Okazaki fragments are short stretches of newly synthesized DNA that are separated by RNA primers. They are formed by the discontinuous synthesis of DNA on the lagging strand during replication.

References

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References

- Reconstitution of eukaryotic lagging strand DNA replication.
- Timing, coordination, and rhythm: acrobatics at the DNA replication fork.

Genetics	General Principles	Dna replication
Subject	System	Topic

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A 1-hour-old girl born to a 40-year-old woman is brought to the nursery for evaluation. The pregnancy and delivery were uncomplicated. Physical examination shows mid-face hypoplasia with a flat nasal bridge, up-slanting palpebral fissures, a small mouth, and a single palmar crease bilaterally. Cardiac auscultation reveals a blowing holosystolic murmur heard best along the sternal border. Which of the following abnormalities is most likely to be present in this patient?

A. Aberrant genomic imprinting
B. Mosaicism
C. Partial deletion
D. Triplet expansion
E. Uniparental disomy

Submit

A 1-hour-old girl born to a 40-year-old woman is brought to the nursery for evaluation. The pregnancy and delivery were uncomplicated. Physical examination shows mid-face hypoplasia with a flat nasal bridge, up-slanting palpebral fissures, a small mouth, and a single palmar crease bilaterally. Cardiac auscultation reveals a blowing holosystolic murmur heard best along the sternal border. Which of the following abnormalities is most likely to be present in this patient?

- A. Aberrant genomic imprinting (2%)
- ✓ B. Mosaicism (46%)
- C. Partial deletion (5%)
- D. Triplet expansion (12%)
- E. Uniparental disomy (33%)

Omitted
Correct answer
B

46%
Answered correctly

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04/08/2020
Last Updated

Explanation

Inheritance of Down syndrome		
Mechanism	Pathogenesis	Recurrence risk

Inheritance of Down syndrome		
Mechanism	**Pathogenesis**	**Recurrence risk**
Meiotic nondisjunction (~95%)	• Extra copy of chromosome 21 present in every cell	Based on maternal age
Unbalanced translocation	• All or part of additional chromosome 21 **attached** to another chromosome	**High** if balanced translocation is present in one parent
Mosaicism	• **Some** (not all) cells have an extra copy of chromosome 21 • Nondisjunction event in early embryonic life	Similar to normal population

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This child has many of the characteristic features of Down syndrome (DS), a condition that results from an **increased gene dosage** effect due to an **extra copy** of chromosome 21. Three cytogenetic abnormalities can lead to DS:

- Meiotic nondisjunction accounts for nearly 95% of DS cases. Failure of homologous chromosomes or sister chromatids to separate during meiosis can result in the inheritance of 3 copies of chromosome 21 in one daughter cell (trisomy) and 1 copy in the other daughter cell (monosomy). Nondisjunction during meiosis is almost always of maternal origin.
- **Unbalanced translocations** account for 2%-3% of DS cases. These individuals have 46 chromosomes, but have extra genetic material (consisting of duplicate chromosome 21 genes) attached to one of their chromosomes. Approximately one third of these cases are due to a

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- **Unbalanced translocations** account for 2%-3% of DS cases. These individuals have 46 chromosomes, but have extra genetic material (consisting of duplicate chromosome 21 genes) attached to one of their chromosomes. Approximately one third of these cases are due to a balanced translocation in one parent, which confers a high recurrence risk.
- **Mosaicism** accounts for <2% of DS cases. Affected individuals have 2 distinct cell lines as a result of **nondisjunction during mitosis**: one with a normal genotype and one with trisomy 21. The proportion of affected cells determines the severity of DS features.

Of the available answer options, only mosaicism is consistent with a **third copy** of chromosome 21 existing in at least a portion of the patient's cells.

(Choices A and E) Genomic imprinting is a normal process that refers to selective activation of gene expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when a person receives **2 copies** of a chromosome from the same parent and no copy from the other parent. Prader-Willi syndrome and Angelman syndrome (15q) are examples of conditions caused by dysfunctional imprinting due to uniparental disomy.

(Choice C) Many genetic syndromes are caused by deletions (loss of genetic material). Cri du chat syndrome (5p deletion) is an example of a syndrome caused by a partial deletion of chromosome 5.

(Choice D) Increased trinucleotide repeats (triplet expansion) on certain genes can lead to silencing of a gene or synthesis of an abnormal gene product. Huntington disease and fragile X syndrome are examples of conditions caused by triplet expansion.

Educational objective:

Common findings in Down syndrome include cognitive impairment, facial dysmorphism, and cardiac defects; 95% of cases are caused by the

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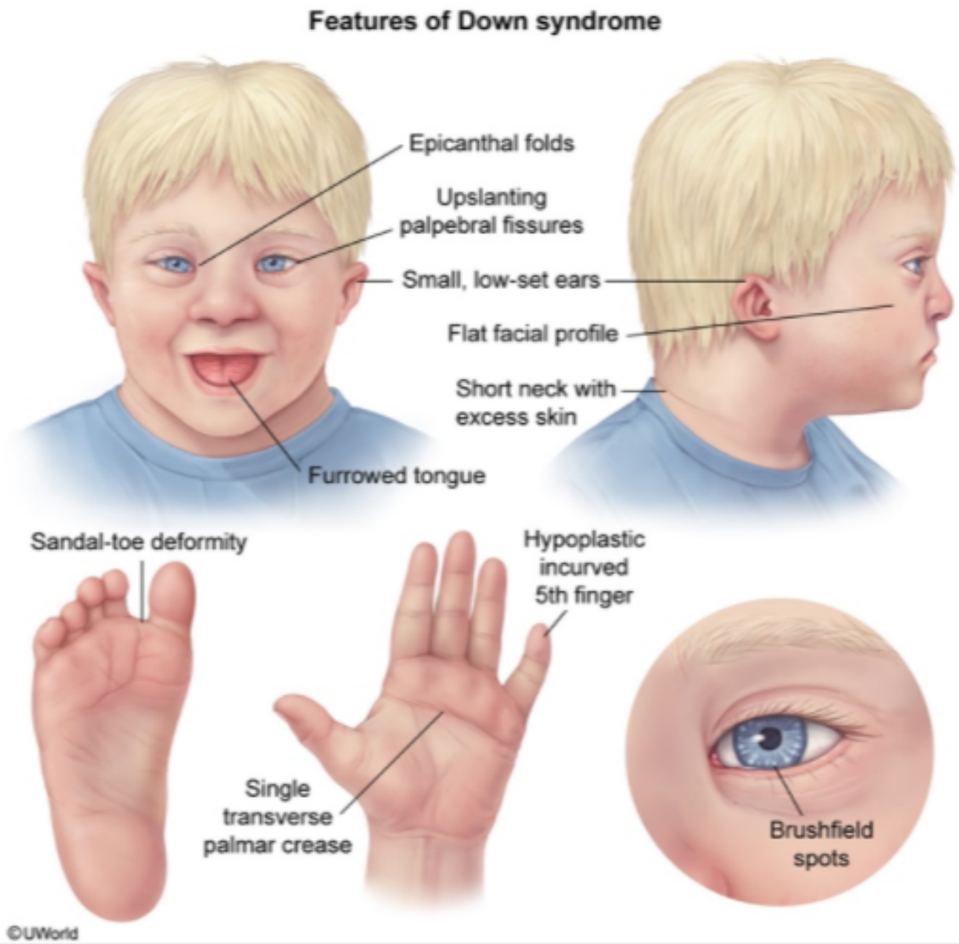

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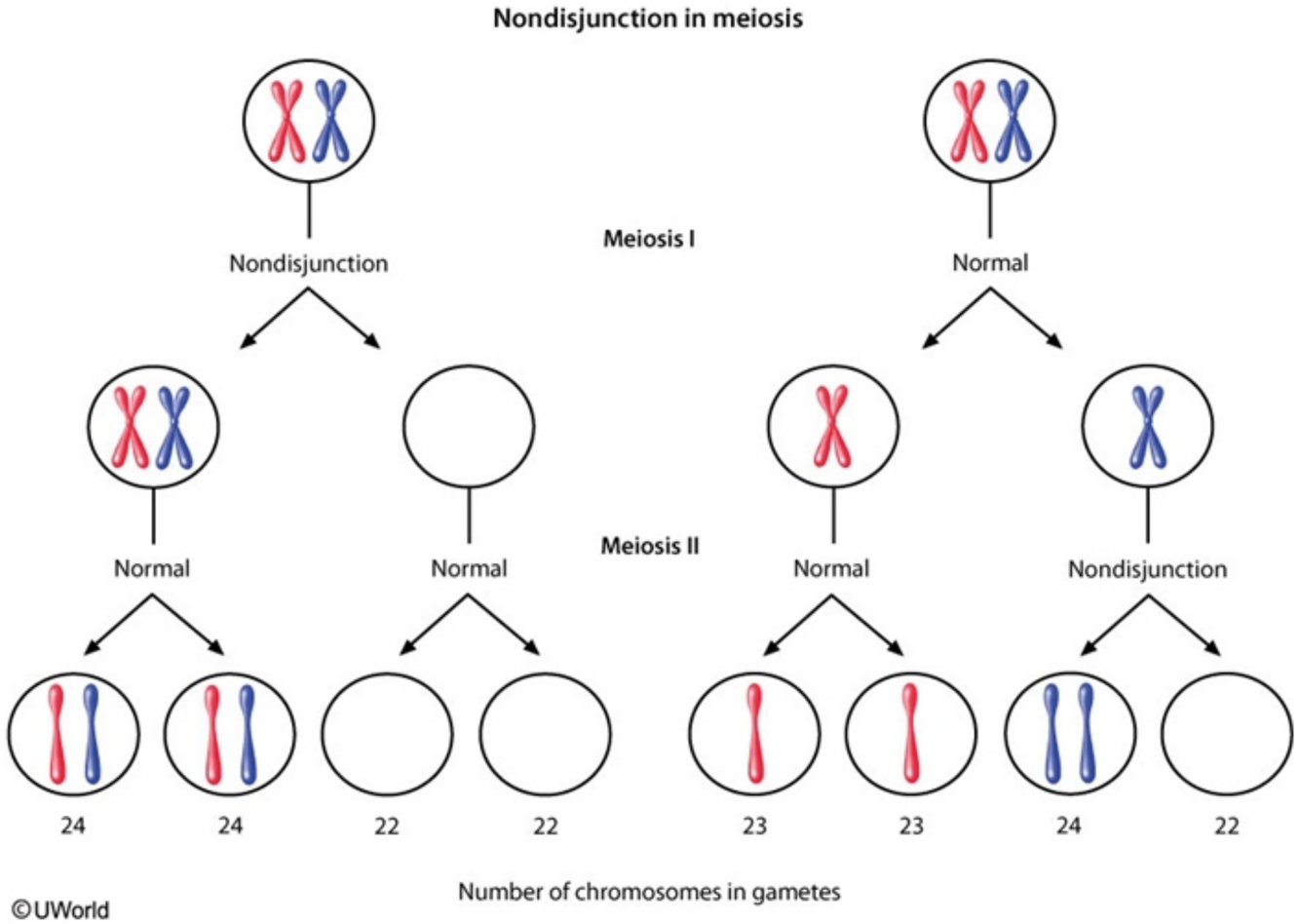

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Of the available answer options, only mosaicism is consistent with a **third copy** of chromosome 21 existing in at least a portion of the patient's cells.

(Choices A and E) Genomic imprinting is a normal process that refers to selective activation of gene expression depending on the parent of origin. Aberrant imprinting occurs with uniparental disomy, or when a person receives **2 copies** of a chromosome from the same parent and no copy from the other parent. Prader-Willi syndrome and Angelman syndrome (15q) are examples of conditions caused by dysfunctional imprinting due to uniparental disomy.

(Choice C) Many genetic syndromes are caused by deletions (loss of genetic material). Cri du chat syndrome (5p deletion) is an example of a syndrome caused by a partial deletion of chromosome 5.

(Choice D) Increased trinucleotide repeats (triplet expansion) on certain genes can lead to silencing of a gene or synthesis of an abnormal gene product. Huntington disease and fragile X syndrome are examples of conditions caused by triplet expansion.

Educational objective:
Common findings in Down syndrome include cognitive impairment, facial dysmorphism, and cardiac defects; 95% of cases are caused by the presence of an extra chromosome 21 (trisomy) resulting from nondisjunction. Unbalanced Robertsonian translocations or mosaicism are less common causes.

References

- A parent's guide to the genetics of Down syndrome.
- Mosaicism for trisomy 21: a review.

Genetics	General Principles	Aneuploidy
Subject	System	Topic

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A 6-year-old boy is brought to the office due to a persistent facial ulcer for the past 2 months. His mother reports that the patient has extreme sensitivity to sunlight and has developed freckles on his face, neck, and limbs since infancy. On physical examination, the skin in sun-exposed areas is dry and rough with numerous freckles and erythematous macules. There is an ulcerated plaque on the left face; a biopsy reveals squamous cell carcinoma. Further testing leads to a diagnosis of xeroderma pigmentosum. A defect in which of the following enzymes is most likely causing this patient's condition?

A. 3'→5' exonuclease

B. DNA ligase

C. Endonuclease

D. Helicase

E. Topoisomerase

Submit

A 6-year-old boy is brought to the office due to a persistent facial ulcer for the past 2 months. His mother reports that the patient has extreme sensitivity to sunlight and has developed freckles on his face, neck, and limbs since infancy. On physical examination, the skin in sun-exposed areas is dry and rough with numerous freckles and erythematous macules. There is an ulcerated plaque on the left face; a biopsy reveals squamous cell carcinoma. Further testing leads to a diagnosis of xeroderma pigmentosum. A defect in which of the following enzymes is most likely causing this patient's condition?

- A. 3'→5' exonuclease (33%)
- B. DNA ligase (4%)
- ✓ C. Endonuclease (58%)
- D. Helicase (0%)
- E. Topoisomerase (2%)

Omitted
Correct answer
C

58%
Answered correctly

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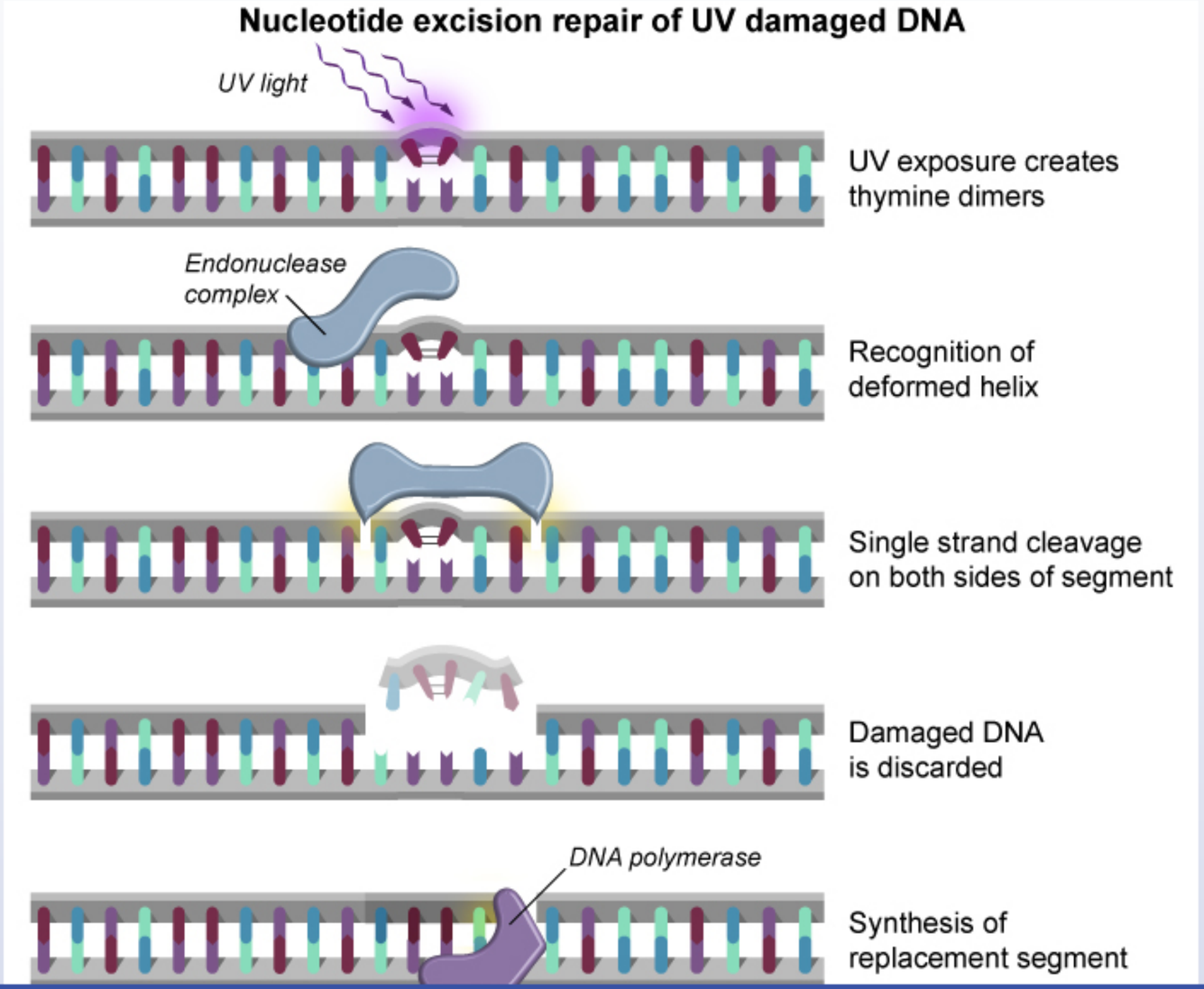
Last Updated

Explanation

Explanation



Explanation

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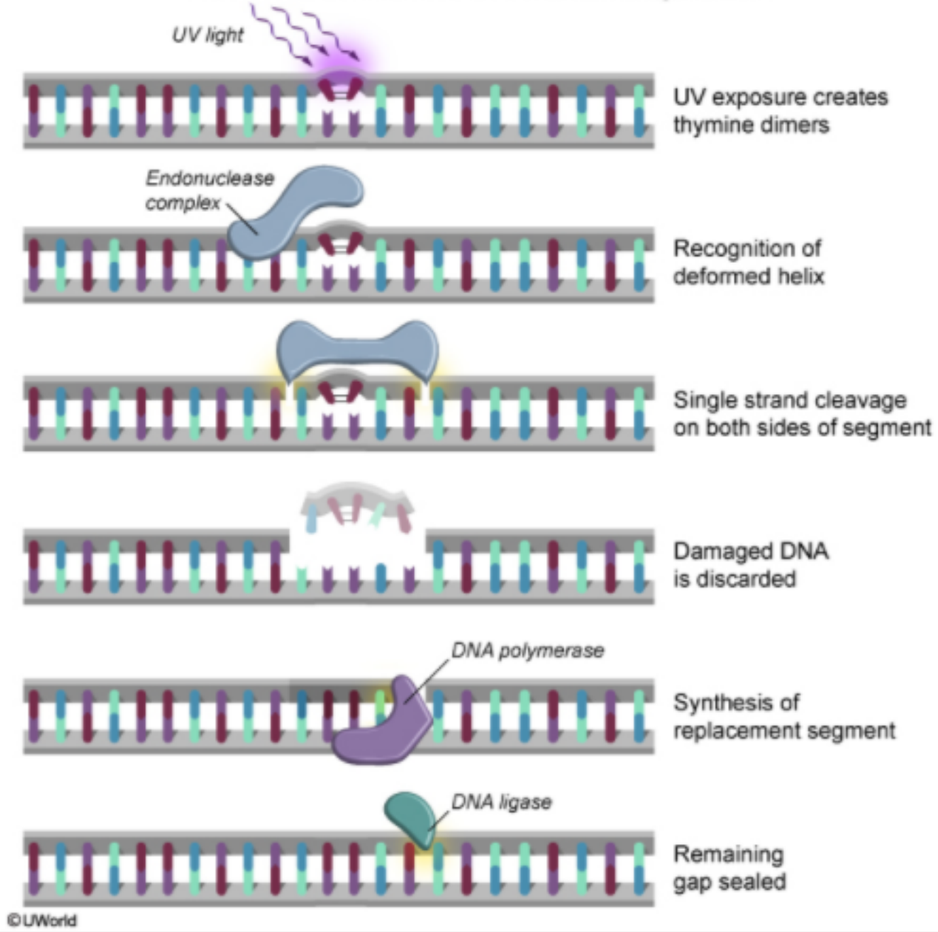
Nucleotide excision repair of UV damaged DNA



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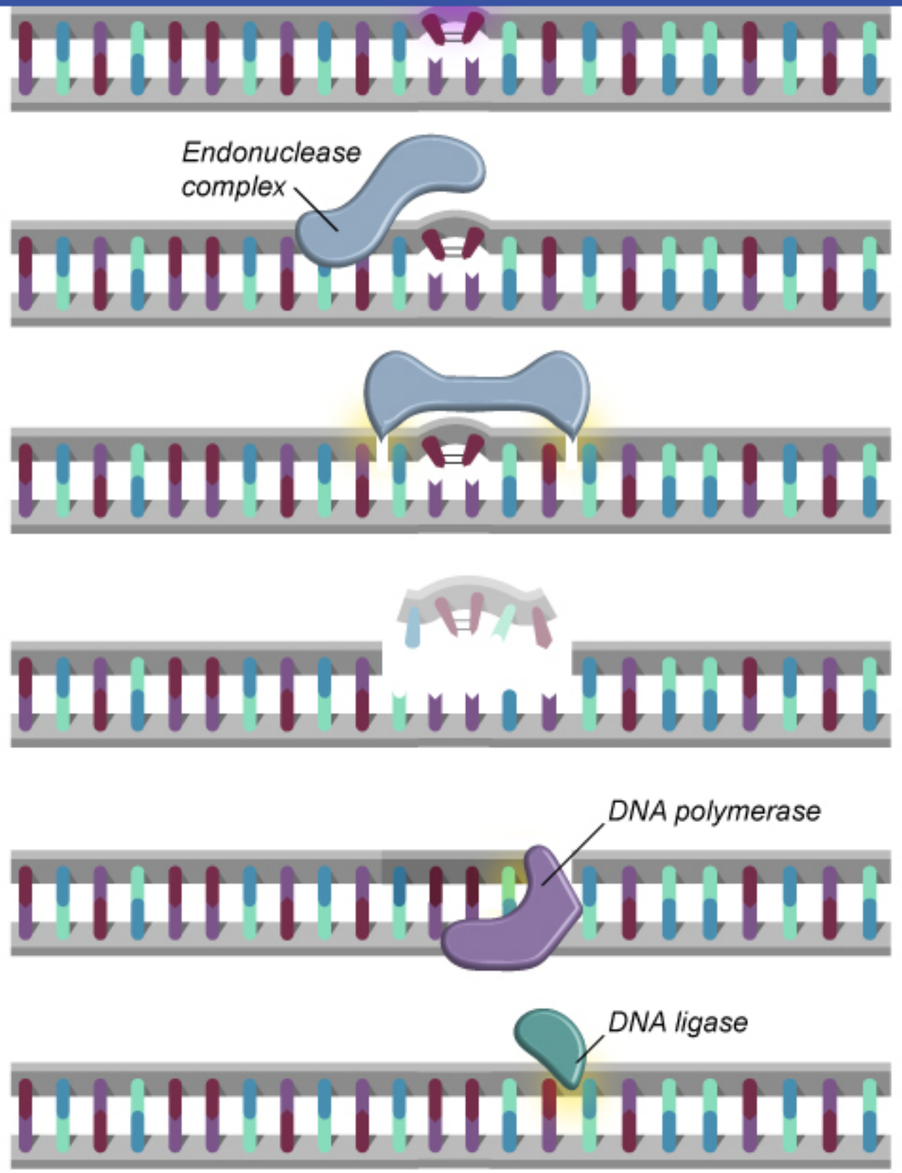

UV exposure creates thymine dimers

Recognition of deformed helix

Single strand cleavage on both sides of segment

Damaged DNA is discarded

Synthesis of replacement segment

Remaining gap sealed

This boy with severe photosensitivity, poikiloderma, hyperpigmentation in sun-exposed areas, and squamous cell carcinoma of the skin has **xeroderma pigmentosum**, an autosomal recessive disorder characterized by defects in **nucleotide excision repair**.

DNA can be damaged by **ultraviolet rays**, leading to formation of **thymine dimers** between 2 adjacent thymine residues. These thymine dimers are repaired by **UV-specific endonuclease**, an enzyme that is frequently deficient in patients with xeroderma pigmentosum. This enzyme recognizes distortions in the structure of DNA caused by thymine dimers and subsequently excises stretches of single-stranded DNA that contain these defects. The gap created following this excision is then filled by DNA polymerase, which uses the opposite DNA strand as a template. The new strand of DNA is then joined on both ends to the existing DNA by the enzyme ligase.

(Choice A) 3'→5' exonuclease activity describes the "proofreading" ability of DNA polymerase. This ability allows for the recognition and repair of mismatched bases during DNA replication. Hereditary nonpolyposis colon cancer is associated with DNA mismatch repair gene mutations.

(Choice B) DNA ligase is responsible for creating a phosphodiester linkage between the phosphate group of the 5' end of a DNA fragment and the hydroxyl group of the 3' end. DNA ligase is particularly active in joining the Okazaki fragments created during discontinuous replication of the lagging strand.

(Choice D) Helicases are responsible for unwinding and separating double-stranded DNA into single-stranded DNA in preparation for DNA replication.

(Choice E) Topoisomerase enzymes relieve DNA supercoiling produced during unwinding and separation by helicase. Prokaryotic topoisomerase II (DNA gyrase) is inhibited by fluoroquinolone antibiotics, whereas eukaryotic topoisomerase II is inhibited by the anticancer drug etoposide.

Educational objective:
Xeroderma pigmentosum is an autosomal recessive disorder characterized by defective nucleotide excision repair often caused by a deficiency in UV-specific endonuclease. Affected children usually have severe photosensitivity, hyperpigmentation in sun-exposed areas, and a greatly increased risk for skin cancer.

References

- Xeroderma pigmentosum.

A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient has no medical problems other than a history of cleft lip, which was repaired in childhood. Her husband is healthy, but her previous child was born with spina bifida. She takes a daily prenatal vitamin. Physical examination is unremarkable and uterine size is in accordance with ultrasound dates. The patient is worried that the fetus may develop the same birth defect as her previous child. Which of the following is the most likely mode of inheritance of this disorder?

- A. Autosomal dominant
- B. Autosomal recessive
- C. Mitochondrial
- D. Multifactorial
- E. X-linked recessive

Submit

A 33-year-old woman, gravida 2 para 1, comes to the office for a prenatal visit at 20 weeks gestation. She feels well and reports experiencing fetal movements. The patient has no medical problems other than a history of cleft lip, which was repaired in childhood. Her husband is healthy, but her previous child was born with spina bifida. She takes a daily prenatal vitamin. Physical examination is unremarkable and uterine size is in accordance with ultrasound dates. The patient is worried that the fetus may develop the same birth defect as her previous child. Which of the following is the most likely mode of inheritance of this disorder?

- A. Autosomal dominant (5%)
- B. Autosomal recessive (5%)
- C. Mitochondrial (2%)
- ✓ D. Multifactorial (84%)
- E. X-linked recessive (1%)

Omitted
Correct answer
D

84%
Answered correctly

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Explanation

Multifactorial inheritance is a term used to describe a complex process by which numerous genetic and environmental factors interact to determine phenotypic expression. Unlike single-gene disorders, diseases displaying multifactorial inheritance make precise genetic analysis and counseling extremely challenging due to their intricate development process. What is understood about these diseases is that the **closer a relative** is to the affected person, the **more likely** the relative is to develop the trait.

Explanation

Multifactorial inheritance is a term used to describe a complex process by which numerous genetic and environmental factors interact to determine phenotypic expression. Unlike single-gene disorders, diseases displaying multifactorial inheritance make precise genetic analysis and counseling extremely challenging due to their intricate development process. What is understood about these diseases is that the **closer a relative** is to the affected person, the **more likely** the relative is to develop the trait.

Spina bifida is an example of a multifactorial condition. There are a multitude of different genes that play a role in neurulation, the process responsible for formation of the neural tube. In addition to genetic factors, a number of environmental factors have profound effects on neural tube development; the most well known is dietary folate deficiency. Neural tube defects are more common in first-degree relatives of those affected, with a recurrence risk of 2%-5%. In general, most multifactorial conditions have a lower recurrence risk than autosomal dominant and autosomal recessive diseases, which convey a 50% and 25% risk to first-degree family members, respectively.

Other examples of multifactorial diseases include cleft lip and palate, diabetes mellitus, coronary artery disease, and hypertension.

(Choice A) A condition inherited in an autosomal dominant pattern will be expressed in 50% of offspring when 1 parent is affected. Classic examples include Huntington disease, Marfan syndrome, multiple endocrine neoplasias, and the neurofibromatoses.

(Choice B) A condition inherited in an autosomal recessive fashion will be expressed in 25% of offspring when both parents are carriers. Cystic fibrosis, hemochromatosis, and sickle cell anemia are examples of autosomal recessive diseases.

(Choice C) Humans inherit mitochondrial DNA only from their mothers; therefore, mitochondrial inheritance is purely maternal. Disorders transmitted via mitochondrial inheritance display variable expressivity, meaning that severity of phenotypic expression can differ greatly even among close relatives. Examples of mitochondrial diseases are myoclonic epilepsy and Leber hereditary optic neuropathy.

(Choice E) X-linked recessive inheritance refers to a trait that is passed via the X chromosome in a recessive manner. Phenotypic expression in offspring is dependent on the sex of the child; all males who inherit the X chromosome will display the phenotype whereas only homozygous females will display the phenotype. Examples include Duchenne and Becker muscular dystrophy, hemophilia, and G6PD deficiency.

Educational objective:
Many frequently encountered diseases (eg, hypertension, spinal bifida) display multifactorial inheritance, which involves the complex interaction of

Explanation

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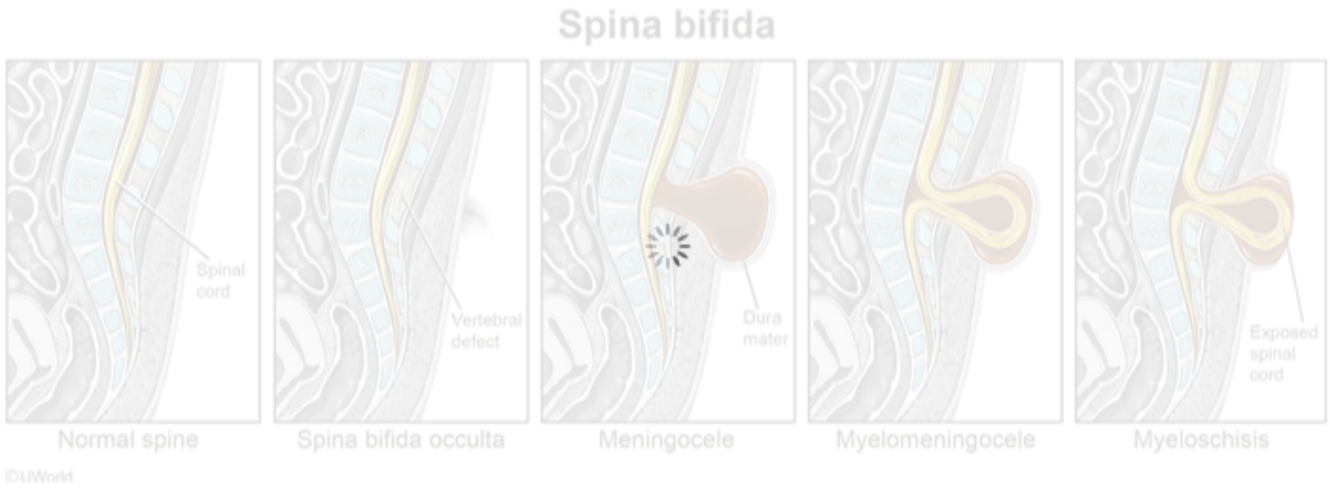

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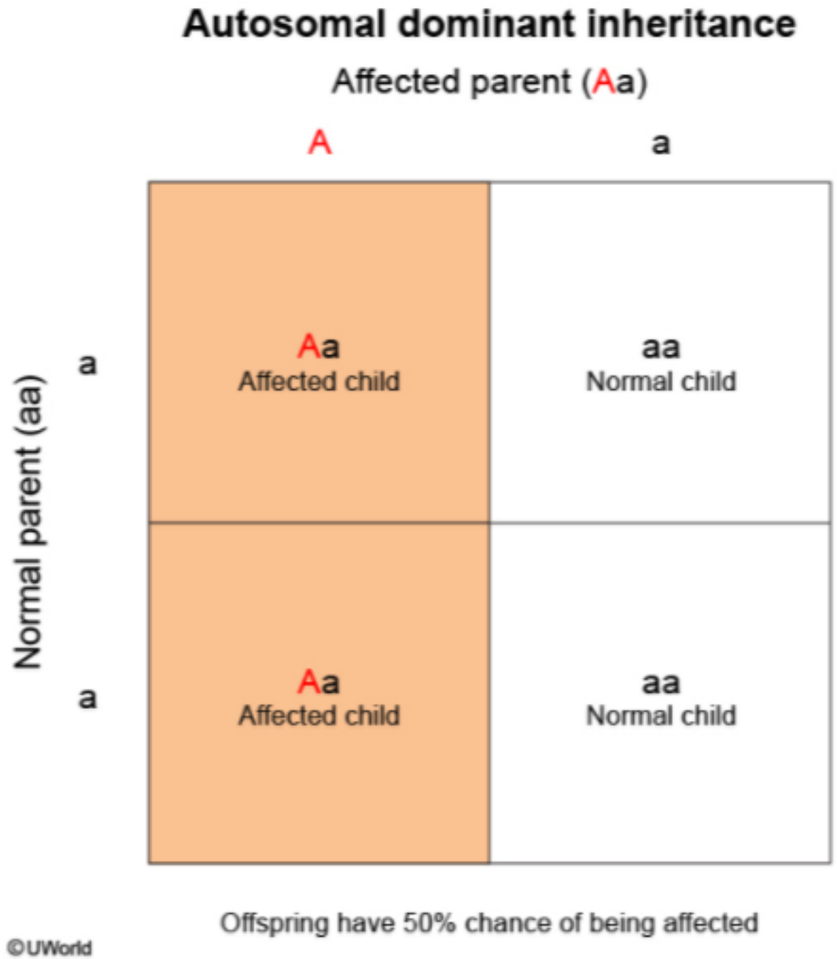

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Explanation

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Autosomal recessive inheritance

Carrier parent (Aa)

Carrier parent (Aa)	A	a
A	AA Normal child	Aa Carrier child
a	Aa Carrier child	aa Affected child

Offspring have 25% chance of being affected

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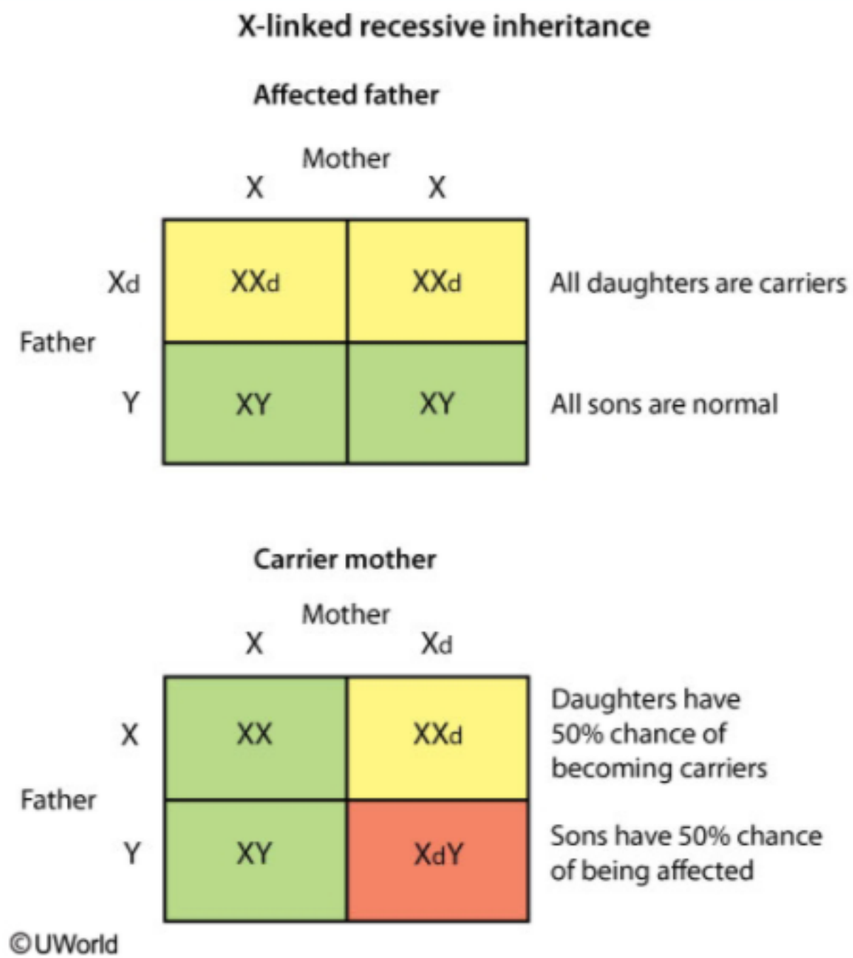

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A 12-year-old girl is brought to the physician by her parents, who are concerned about her loss of interest in playing sports at school. During a recent competition, she walked off the field in the middle of the game, complaining about the pain in her legs. The patient has no other medical conditions and takes no medications. Her vaccination schedule is up-to-date. Physical examination shows pulsatile vessels within the intercostal spaces and diminished femoral pulses relative to brachial pulses. This patient's symptoms are most likely associated with which of the following conditions?

- A. DiGeorge syndrome
- B. Down syndrome
- C. Friedreich ataxia
- D. Kartagener syndrome
- E. Marfan syndrome
- F. Tuberous sclerosis
- G. Turner syndrome

Submit

A 12-year-old girl is brought to the physician by her parents, who are concerned about her loss of interest in playing sports at school. During a recent competition, she walked off the field in the middle of the game, complaining about the pain in her legs. The patient has no other medical conditions and takes no medications. Her vaccination schedule is up-to-date. Physical examination shows pulsatile vessels within the intercostal spaces and diminished femoral pulses relative to brachial pulses. This patient's symptoms are most likely associated with which of the following conditions?

- A. DiGeorge syndrome (2%)
- B. Down syndrome (1%)
- C. Friedreich ataxia (3%)
- D. Kartagener syndrome (2%)
- E. Marfan syndrome (6%)
- F. Tuberous sclerosis (5%)
- ✓ G. Turner syndrome (78%)

Omitted
Correct answer
G

78%
Answered correctly

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Last Updated

Explanation

Selected inherited disorders & associated cardiovascular developmental defects	
Disease	**Cardiovascular abnormalities**
Down syndrome	• Endocardial cushion defects (eg, ostium primum atrial septal defects, regurgitant atrioventricular valves)
DiGeorge syndrome	• Tetralogy of Fallot • Interrupted aortic arch
Friedreich ataxia	• Hypertrophic cardiomyopathy
Kartagener syndrome	• Situs inversus
Marfan syndrome	• Cystic medial necrosis (eg, aortic dissection & aneurysm) • Mitral valve prolapse

Exhibit Display

Selected inherited disorders & associated cardiovascular developmental defects	
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Marfan syndrome	• Cystic medial necrosis (eg, aortic dissection & aneurysm) • Mitral valve prolapse
Tuberous sclerosis	• Valvular obstruction due to cardiac rhabdomyomas
Turner syndrome	• Aortic coarctation • Bicuspid aortic valve

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Friedreich ataxia	• Hypertrophic cardiomyopathy
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Marfan syndrome	• Cystic medial necrosis (eg, aortic dissection & aneurysm) • Mitral valve prolapse
Tuberous sclerosis	• Valvular obstruction due to cardiac rhabdomyomas
Turner syndrome	• Aortic coarctation • Bicuspid aortic valve

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This patient most likely has congenital coarctation of the aorta, which typically affects the region of the aorta just distal to the left subclavian artery. Although traditionally classified into preductal and postductal types, the signs and symptoms of aortic coarctation depend more on the age at presentation, which varies according to the severity of the stenosis. Severe coarctation usually presents in infancy with differential cyanosis affecting the lower extremities as long as the ductus arteriosus remains patent. On ductal closure, these neonates can develop signs of heart failure and shock. More moderate stenosis often presents in childhood or adolescence with symptoms of lower-extremity claudication (eg, pain and cramping with exercise), blood pressure discrepancy between the upper and lower extremities, and delayed or diminished femoral pulses. Continuous murmurs and pulsatile intercostal collaterals can also develop secondary to restricted circulation.

Congenital aortic coarctation occurs in up to 10% of patients with Turner syndrome (45,XO)

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Congenital aortic coarctation occurs in up to 10% of patients with Turner syndrome (45,XO).

(Choice A) DiGeorge syndrome is associated with at least 15% of cases of interrupted aortic arch, a more extreme anomaly than aortic coarctation in which the aortic arch is atretic or a segment of the arch is absent. Affected patients have poor lower-extremity pulses, but respiratory distress, variable cyanosis, and signs of congestive heart failure will also develop during the first days of life.

(Choice B) Down syndrome is associated with endocardial cushion defects that result in ostium primum atrial septal defects and regurgitant atrioventricular valves.

(Choice C) Friedreich ataxia is marked by spinocerebellar degeneration with predominantly spinal ataxia. This can produce difficulty walking, but femoral pulses are not affected. This autosomal recessive condition is associated with hypertrophic cardiomyopathy.

(Choice D) In Kartagener syndrome, cilia are immotile due to a microtubular dynein arm defect. Infertility, recurrent sinusitis, and bronchiectasis occur as a result. This syndrome is associated with situs inversus, not aortic coarctation.

(Choice E) Marfan syndrome is associated with cystic medial necrosis of the aorta, which may result in aortic dissection and aortic valve incompetence. Mitral valve prolapse can also occur due to the same degenerative process.

(Choice F) Tuberous sclerosis is an autosomal dominant syndrome characterized by cutaneous angiofibromas (adenoma sebaceum), seizures, and mental retardation. Pathological lesions include central nervous system hamartomas and benign neoplasms, renal and other visceral cysts, and cardiac rhabdomyomas.

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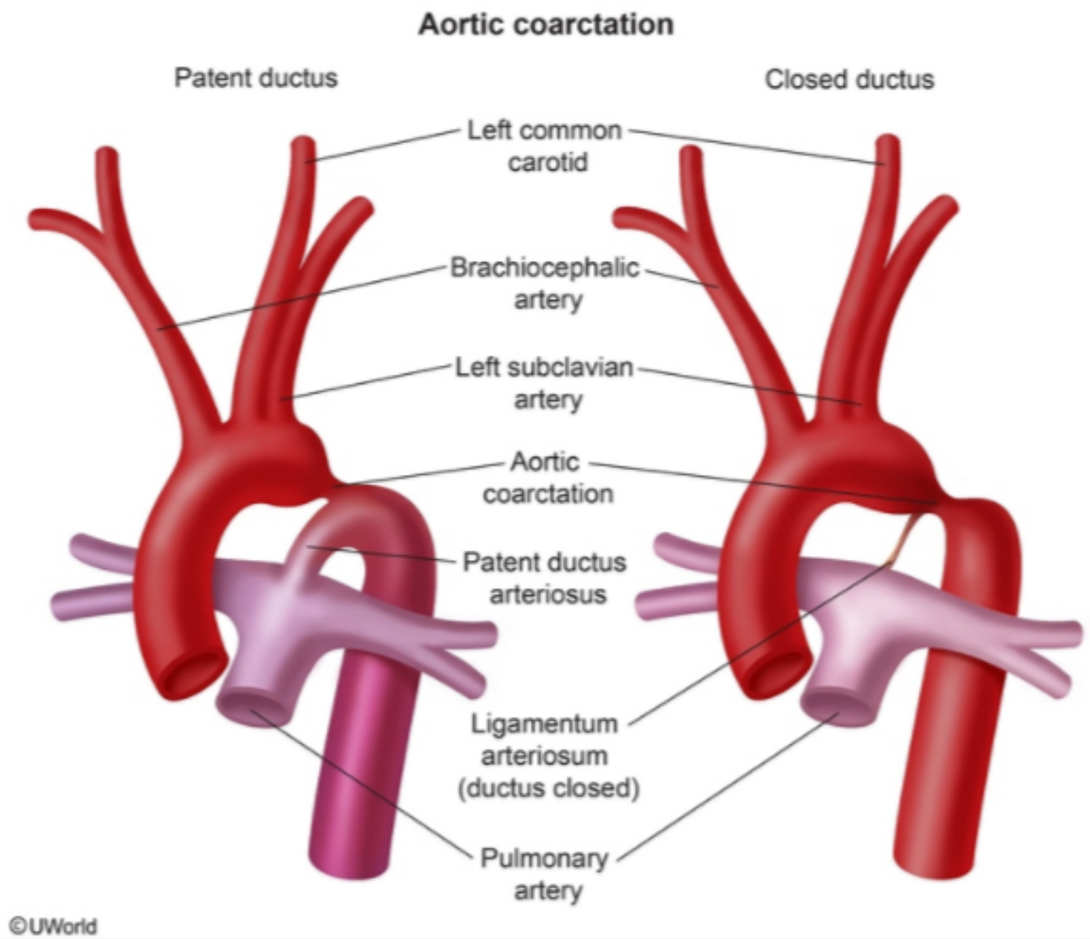

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Congenital aortic coarctation occurs in up to 10% of patients with Turner syndrome (45,XO).

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Educational objective:
Aortic coarctation in a child/young adult presents with lower-extremity claudication (eg, pain and cramping with exercise), blood pressure discrepancy between the upper and lower extremities, and delayed or diminished femoral pulses. Turner syndrome (45,XO) is associated with coarctation of the aorta in up to 10% of cases.

Genetics	Cardiovascular System	Turner syndrome
Subject	System	Topic

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A 28-year-old man is evaluated for abnormal movements of the hands and face. The patient reports that he started experiencing involuntary grimacing a year ago, which has gradually worsened. He is taking a selective serotonin reuptake inhibitor for major depression but has not taken any antipsychotic medications. His 52-year-old father was diagnosed with an inherited movement disorder 2 months ago. Physical examination shows normal strength and normal deep tendon reflexes. No sensory deficits are noted. Which of the following best explains the difference in disease presentation between this patient and his father?

A. Anticipation
B. Genomic imprinting
C. Incomplete penetrance
D. Microdeletion
E. Mosaicism
F. Pleiotropy

Submit

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- ✓ A. Anticipation (88%)
- B. Genomic imprinting (0%)
- C. Incomplete penetrance (5%)
- D. Microdeletion (0%)
- E. Mosaicism (1%)
- F. Pleiotropy (2%)

Omitted
Correct answer
A

88%
Answered correctly

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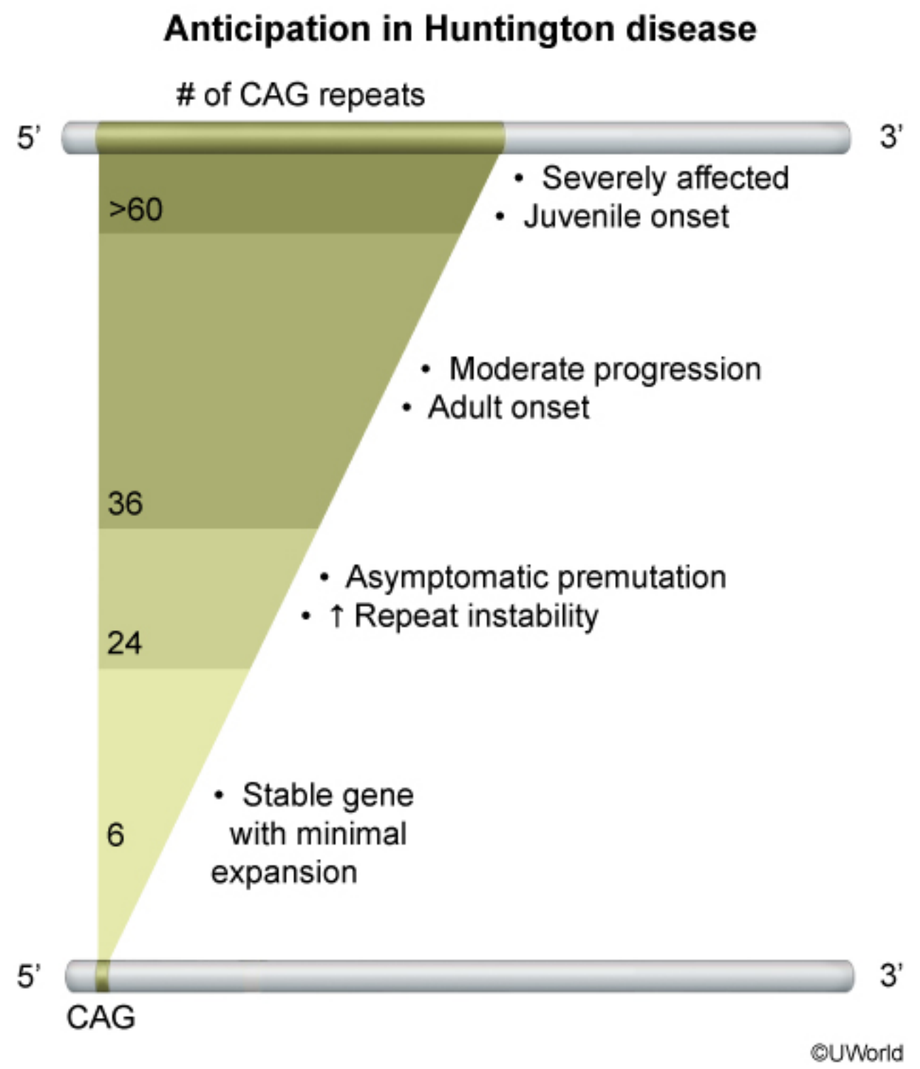
Explanation

Anticipation in Huntington disease

# of CAG repeats



This patient presenting with involuntary movements, depression, and a family history of a movement disorder likely has **Huntington disease** (HD), which typically manifests with the triad of movement disorder (chorea), behavioral abnormalities (aggressiveness, apathy, or depression), and

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This patient presenting with involuntary movements, depression, and a family history of a movement disorder likely has **Huntington disease** (HD), which typically manifests with the triad of movement disorder (chorea), behavioral abnormalities (aggressiveness, apathy, or depression), and dementia. HD is caused by an expansion of cytosine-adenine-guanine (CAG) trinucleotide repeats. Most patients develop symptoms in their 40s or 50s, but an earlier age of onset and more severe symptoms are associated with a larger number of **trinucleotide repeats**.

During spermatogenesis, CAG repeats in the abnormal *HTT* gene (chromosome 4p) can rapidly increase (much more than during oogenesis). Therefore, patients who receive an abnormal gene from their fathers tend to develop the disease earlier in life. The tendency for clinical symptoms to worsen and/or occur earlier in subsequent generations is called **anticipation**. Anticipation is common in disorders associated with trinucleotide repeats, as in Fragile X syndrome, myotonic dystrophy, and Friedreich ataxia.

(Choice B) Genomic imprinting is a selective inactivation of the genes of either maternal or paternal origin. It results in Prader-Willi and Angelman syndromes, which involve deletions of the same region on chromosome (15q) but have very different clinical manifestations due to the differential expression of parental genes. When the chromosome with the deleted region comes from the father, the lack of expression of maternally imprinted genes results in Prader-Willi syndrome. Likewise, deletions affecting the maternal chromosome result in Angelman syndrome due to absent expression of paternally imprinted genes.

(Choice C) HD is transmitted in an autosomal dominant pattern with complete penetrance, which means that a child who inherits the abnormal gene will inevitably develop Huntington disease.

(Choice D) Microdeletion is the loss of genetic material too small to be visible via light microscopy. For example, microdeletion of 22q11 is responsible for DiGeorge syndrome.

(Choice E) The presence of 2 populations of cells with different genotypes in one patient resulting in the mixed expression of disease is called mosaicism. Examples of mosaicism include milder forms of Turner (genotype 46XX/45X0), Klinefelter (46XY/47XXY), and Down syndromes.

(Choice F) Sometimes, one gene mutation leads to multiple, seemingly unrelated phenotypic abnormalities, a genetic phenomenon termed pleiotropy.

Educational objective:
An increased number of trinucleotide repeats on the *HTT* gene is associated with Huntington disease. The larger the number of repeats, the

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Educational objective:
An increased number of trinucleotide repeats on the *HTT* gene is associated with Huntington disease. The larger the number of repeats, the earlier the onset of the disease. Trinucleotide expansion occurs more frequently during paternal transmission, causing a genetic phenomenon called anticipation.

References

- Genetics and neuropathology of Huntington's disease.

Genetics	General Principles	Huntington disease
Subject	System	Topic

A 34-year-old woman comes to the office due to dysuria. The patient has a history of recurrent urinary tract infections. A urine sample is collected and sent for culture. Gram-negative bacteria isolated from the urine are found to form pink colonies on lactose-containing MacConkey agar. Several days later, bacterial isolates from a second urine sample are found to form white colonies when plated on the same type of medium. Genetic analysis shows that the more recent isolates have a single nucleotide deletion within the *lac* operon DNA sequence. This genomic change is most consistent with which of the following?

A. Conservative mutation
B. Frameshift mutation
C. Missense mutation
D. Nonsense mutation
E. Silent mutation

Submit

A 34-year-old woman comes to the office due to dysuria. The patient has a history of recurrent urinary tract infections. A urine sample is collected and sent for culture. Gram-negative bacteria isolated from the urine are found to form pink colonies on lactose-containing MacConkey agar. Several days later, bacterial isolates from a second urine sample are found to form white colonies when plated on the same type of medium. Genetic analysis shows that the more recent isolates have a single nucleotide deletion within the *lac* operon DNA sequence. This genomic change is most consistent with which of the following?

- A. Conservative mutation (5%)
- ✓ B. Frameshift mutation (60%)
- C. Missense mutation (20%)
- D. Nonsense mutation (9%)
- E. Silent mutation (4%)

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Correct answer
B

60%
Answered correctly

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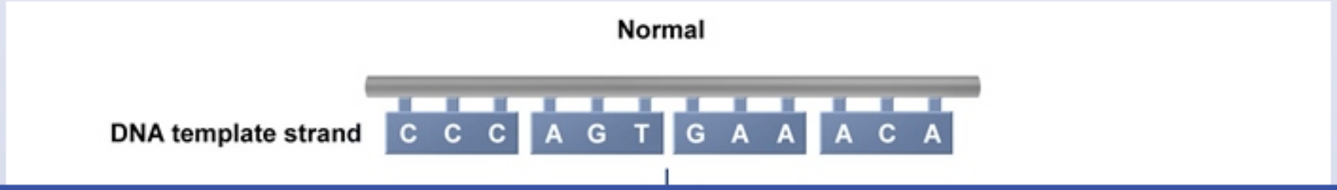
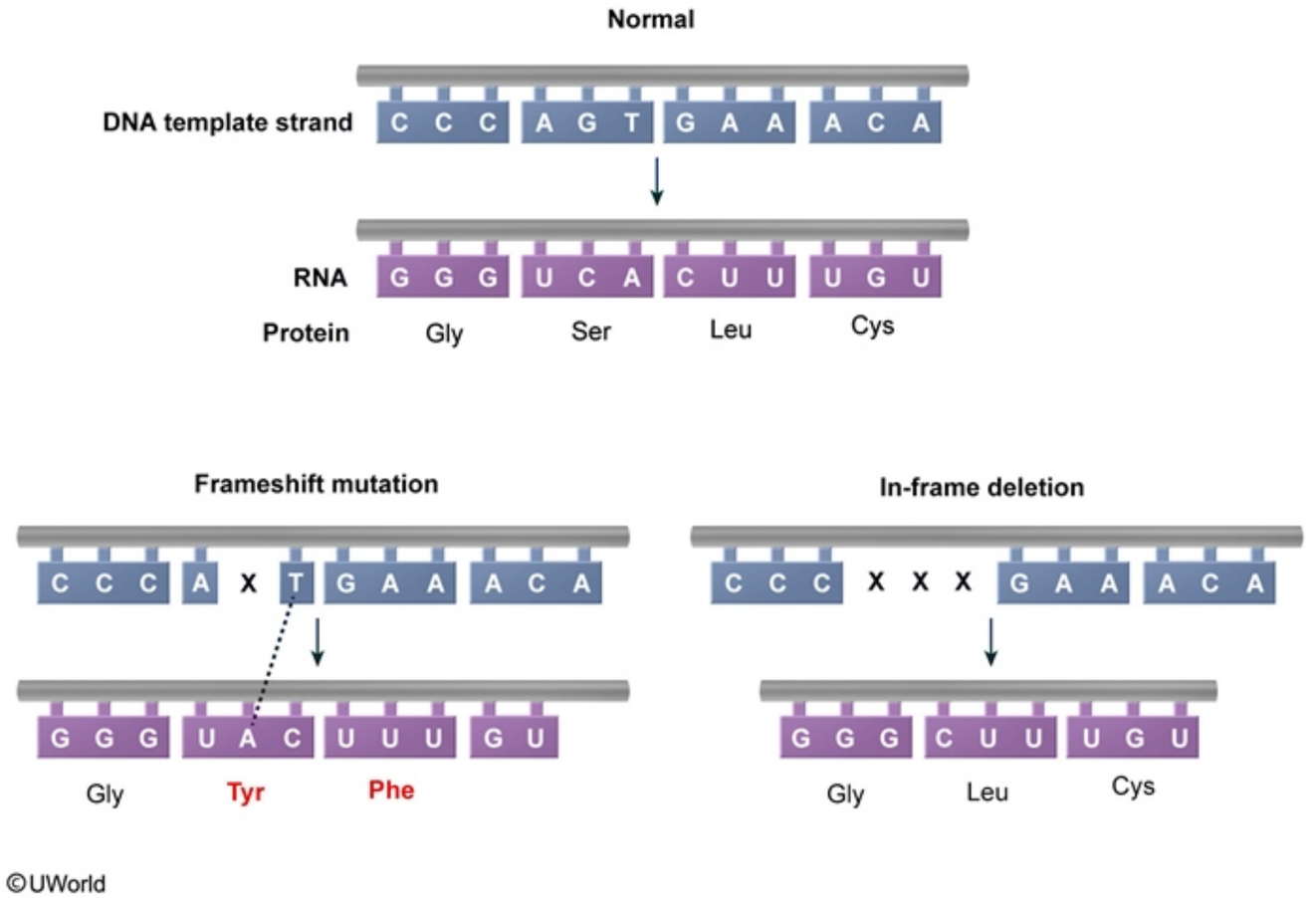
Explanation





Organisms that ferment lactose appear pink on MacConkey agar whereas lactose non-fermenters form white colonies. In this case, the single nucleotide deletion within the *lac* operon DNA sequence of the newer isolates impairs lactose metabolism most likely by preventing the formation of a required enzyme. Because the mutation is a **single base deletion**, it will cause a **frameshift mutation** if it occurs within the coding region (exons) of the gene.

Frameshift mutations are caused by **deletion or insertion** of any number of nucleotides that are **not multiples of 3**. The result is a change in the

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Frameshift mutations are caused by **deletion or insertion** of any number of nucleotides that are **not multiples of 3**. The result is a change in the reading frame during protein translation, which causes the production of an entirely different protein that is often shorter than the original due to formation of a premature stop codon.

The other mutations listed are all examples of point mutations (ie, single base substitutions) that can lead to a variety of changes in the coded protein.

(Choices A and C) Missense mutations are single base substitutions that result in the placement of an incorrect amino acid in a protein sequence. These mutations occur within the coding region of a gene and do not alter protein length. A conservative mutation is a type of missense mutation where an amino acid is replaced with another that has similar biochemical characteristics. Conservative mutations generally preserve protein function unless the mutation occurs in a critical region (eg, active site of enzyme).

(Choice D) Nonsense mutations introduce a premature stop codon in a coding region, resulting in the production of a truncated protein. The mutation described is not a nonsense mutation because it was caused by a single base **deletion** (not a base substitution).

(Choice E) A silent mutation is a single base substitution within a codon that does not change the amino acid (due to codon redundancy). Silent mutations have no effect on protein formation or function.

Educational objective:
A frameshift mutation occurs with the deletion/addition of a number of bases not divisible by 3 in the coding region of a gene. Frameshift mutations alter the reading frame of the genetic code, dramatically changing the protein structure and often resulting in the formation of a premature stop codon.

Genetics | General Principles | Mutations

Exhibit Display

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Genetics	General Principles	Mutations
Subject	System	Topic

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A 25-year-old Caucasian man is undergoing evaluation for azoospermia. The patient has been monogamous with his long-term girlfriend and does not use contraception during sexual intercourse. They have been trying to conceive for the past year with no success. The patient has a past medical history of recurrent pneumonia with frequent hospitalizations for antibiotic treatment. He takes no medications and does not use tobacco, alcohol, or illicit drugs. The patient has no allergies and his immunizations are up-to-date. His family history is unknown as he was adopted as an infant. Physical examination shows digital clubbing. A transrectal ultrasound shows bilateral absence of the vas deferens. Which of the following tests would most likely confirm the underlying diagnosis of this patient's condition?

A. Chloride level in the sweat

B. Cilia motility of the nasal epithelium

C. Serum alpha-1 antitrypsin level

D. Serum FSH and LH levels

E. Serum IgA levels

F. Serum testosterone levels

Submit

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- ✓ A. Chloride level in the sweat (62%)
- B. Cilia motility of the nasal epithelium (26%)
- C. Serum alpha-1 antitrypsin level (1%)
- D. Serum FSH and LH levels (3%)
- E. Serum IgA levels (0%)
- F. Serum testosterone levels (4%)

Omitted
Correct answer
A

62%
Answered correctly

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Time Spent

03/22/2020
Last Updated

Explanation

Primary ciliary dyskinesia versus cystic fibrosis

Primary ciliary dyskinesia versus cystic fibrosis		
	Primary ciliary dyskinesia	**Cystic fibrosis**
Pathogenesis	• **Dynein arm defect** → abnormal ciliary motion & impaired mucociliary clearance	• Mutation in the ***CFTR* gene** → impaired ion transport
Respiratory tract features	• Chronic sinopulmonary infections • Nasal polyps • Bronchiectasis • Digital clubbing	• Chronic sinopulmonary infections • Nasal polyps • Bronchiectasis • Digital clubbing
Extrapulmonary features	• Situs inversus (50% of cases) • Infertility due to immotile spermatozoa • Normal growth	• Pancreatic insufficiency • Infertility due to absent vas deferens (azoospermia) • Failure to thrive
Diagnosis	• Low nasal nitric oxide levels • Bronchoscopy & electron microscopic visualization of ciliary abnormalities	• Elevated sweat chloride levels • Abnormal nasal transepithelial potential difference • Genetic testing

Primary ciliary dyskinesia versus cystic fibrosis

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Diagnosis	• Low nasal nitric oxide levels • Bronchoscopy & electron microscopic visualization of ciliary abnormalities • Genetic testing	• Elevated sweat chloride levels • Abnormal nasal transepithelial potential difference • Genetic testing

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This patient has a history of recurrent pneumonia, digital clubbing, azoospermia, and bilateral absence of the vas deferens; this is most likely due to **cystic fibrosis (CF)**. Patients with CF have variable severity of lung and pancreatic function. Although most patients have recurrent sinopulmonary infections and pancreatic insufficiency, some patients may have mild disease depending on their underlying mutation. Regardless of lung or pancreas function, virtually all adult men with CF have **azoospermia** and **infertility**. Although spermatogenesis is usually normal, almost all males with CF are unable to secrete semen due to **congenital bilateral absence of the vas deferens (CBAVD)**. ***CFTR* mutations** are likely responsible for abnormal development of Wolffian structures, resulting in vasal agenesis and defective sperm transport.

A diagnosis of CF can be based on **elevated sweat chloride levels**. If the sweat chloride test is equivocal, measurement of **nasal transepithelial potential difference** and genetic testing for *CFTR* mutations should be performed to confirm the diagnosis.

(Choice B) Although, primary ciliary dyskinesia (eg, Kartagener syndrome) can cause recurrent pulmonary infections and digital clubbing, infertility in Kartagener syndrome is usually due to immotile spermatozoa. Abnormal nasociliary motility is a nonspecific finding that is seen most commonly in patients with primary ciliary dyskinesia and in some patients with CF (due to abnormally thick mucus). A more specific test for CF is the nasal transepithelial potential difference. In addition, CBAVD is virtually pathognomonic for a *CFTR* mutation.

(Choice C) Low serum alpha-1 antitrypsin (AAT) is associated with AAT deficiency and not with CF. AAT deficiency is typically associated with panacinar emphysema and chronic liver disease. Infertility is not seen in these patients.

(Choices D and F) FSH, LH, and testosterone levels are usually normal in patients with CF. A low testosterone level in the setting of decreased FSH and LH is seen in hypogonadotropic hypogonadism (eg, Kallmann syndrome).

(Choice E) Primary humoral deficiencies usually manifest as recurrent upper and lower respiratory tract infections due to impaired antibody production. However, most patients with selective IgA deficiency are asymptomatic.

Educational objective:
CFTR gene mutations are the most common cause of congenital bilateral absence of the vas deferens (CBAVD). Patients with CBAVD have azoospermia and infertility but normal levels of FSH, LH, and testosterone. Elevated sweat chloride levels are diagnostic of cystic fibrosis.

References

- Management of male infertility due to congenital bilateral absence of vas deferens should not ignore the diagnosis of cystic fibrosis.
- CFTR mutations in men with congenital bilateral absence of the vas deferens (CBAVD): a systemic review and meta-analysis

A 46-year-old woman is evaluated for a 2-month history of progressive abdominal distension, vague abdominal discomfort, and a bloating sensation. Physical examination shows moderate ascites. Laboratory evaluation reveals markedly elevated CA-125 and imaging studies show an ovarian mass. Molecular analysis of the malignant cells in ascitic fluid is performed, and these cells are found to have high telomerase activity. This enzyme promotes cell growth and malignancy by directly causing which of the following actions?

A. Enhancing tissue invasion and metastasis

B. Increasing transcription factor expression

C. Preventing chromosomal shortening

D. Promoting G1/S progression

E. Sustaining angiogenesis

Submit

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- A. Enhancing tissue invasion and metastasis (1%)
- B. Increasing transcription factor expression (2%)
- ✓ C. Preventing chromosomal shortening (91%)
- D. Promoting G1/S progression (3%)
- E. Sustaining angiogenesis (0%)

Omitted
Correct answer
C

91%
Answered correctly

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Time Spent

03/04/2020
Last Updated

Explanation

Telomeres lie at the end of linear eukaryotic chromosomes and have tandem **repeat DNA sequences**, usually GT-rich repeats (eg, TTAGGG). They protect chromosomes from being recognized as damaged DNA, help to regulate gene expression, and participate in controlling cell replication and entry into senescence. As DNA polymerase cannot fully replicate the 3' end of the lagging chromosomal strands, cell division and aging lead to progressive DNA loss and telomere shortening at chromosomal ends. Once cells reach their maximum limit for proliferation (~50-70 divisions), the shortened telomeres trigger permanent growth arrest. Cell checkpoint genes (eg, *TP53*) become activated, and the critically short and dysfunctional telomeres lead to programmed cell death (apoptosis).

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Telomerase is an RNA-dependent DNA polymerase that consists of 2 molecules, human telomerase reverse transcriptase (TERT) and telomerase RNA (TR or TERC). Telomerase synthesizes **telomeric DNA sequences** that can replace the lost **chromosomal ends** of the telomeres. As a result, the telomere can divide without reaching a limit. Normal human cells have absent telomerase activity except in cells that need to divide regularly (eg, germ cells, certain adult stem cells). However, >90% of cancer cells contain increased telomerase activity, allowing for continued proliferation without apoptosis.

(Choice A) Matrix metalloproteinases are proteases that degrade extracellular matrix proteins. They also modulate cell signaling by cleaving cell surface receptors, releasing apoptotic ligands, and inactivating chemokines/cytokines. These enzymes generally increase cell proliferation and allow for tissue invasion and metastasis.

(Choice B) Proto-oncogenes often encode proteins involved in signal transduction in response to growth factors. Mutations in these genes can result in constitutive signal activation and increased transcription factor expression, stimulating cellular proliferation.

(Choice D) Cyclin D is a protein that is synthesized during the G1 phase of the cell cycle and helps promote the G1/S phase transition. Increased expression of cyclin D can result in unchecked cellular proliferation.

(Choice E) Vascular endothelial growth factor (VEGF) is a signal protein that helps create new blood vessels after injury. Cancer cells can overexpress VEGF to promote angiogenesis and allow for increased growth and metastasis.

Educational objective:
Telomerase is an RNA-dependent DNA polymerase that synthesizes telomeric DNA sequences that can replace the lost chromosomal ends of the telomeres. Cancer cells typically contain increased telomerase activity to allow for continued proliferation.

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References

- Progress in structural studies of telomerase.

Genetics	Hematology & Oncology	Ovarian cancer
Subject	System	Topic

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A 12-year-old boy with mild intellectual disability is brought to the office by his adoptive parents for a routine physical examination. The parents say that the boy is adjusting well to a new school that has increased resources for children with learning disabilities. The patient was adopted as an infant and the birth family's history is unknown. His immunizations are up to date, and he has no allergies. Review of the patient's medical records is notable for cytogenetic studies that showed a small gap near the tip of the long arm of the X chromosome. Which of the following findings are likely to be present on this patient's physical examination?

- A. Arachnodactyly, scoliosis, lens dislocation
- B. Large ears, long face, macroorchidism
- C. Short neck, low-set ears, epicanthic folds
- D. Smooth philtrum, thin vermillion border
- E. Tall stature, gynecomastia, infertility

Submit

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- A. Arachnodactyly, scoliosis, lens dislocation (3%)
- ✓ B. Large ears, long face, macroorchidism (83%)
- C. Short neck, low-set ears, epicanthic folds (4%)
- D. Smooth philtrum, thin vermillion border (3%)
- E. Tall stature, gynecomastia, infertility (5%)

Omitted
Correct answer
B

83%
Answered correctly

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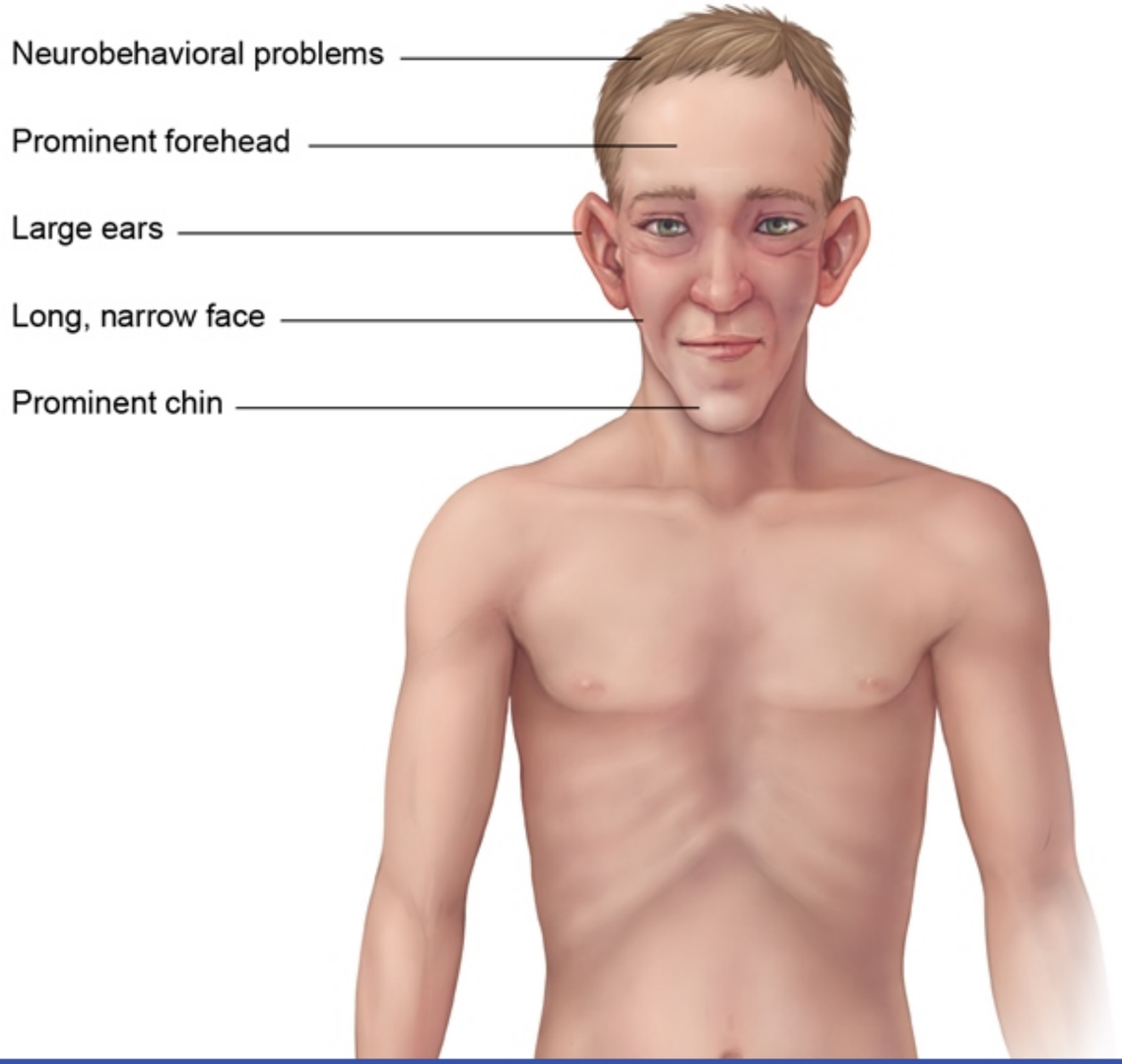
04/22/2020
Last Updated

Explanation

Features of fragile X syndrome



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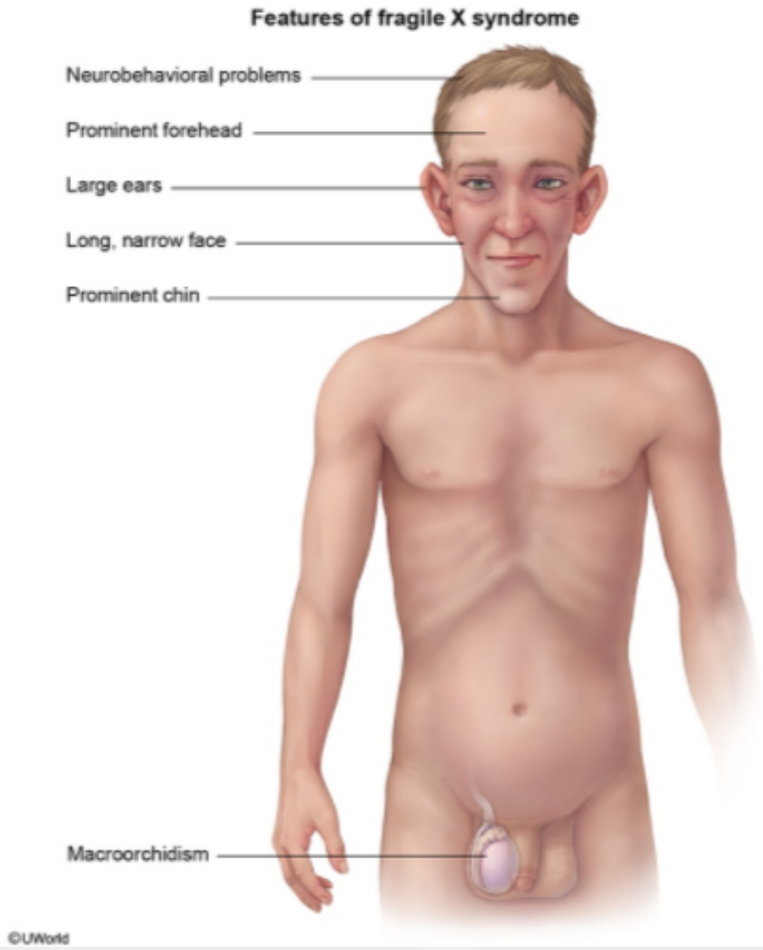

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Fragile X syndrome, an X-linked disorder, is the most common inherited cause of **intellectual disability**. The defect is an unstable **expansion of trinucleotide repeats** (**CGG**) in the fragile X mental retardation 1 (*FMR1*) gene, located on the long arm of the X chromosome. When the cells of affected individuals are cultured in folate-deficient medium, the area of increased repeats does not stain and appears "broken," hence the name "fragile X." Cytogenetic studies (chromosomal analysis) typically show a small gap near the tip of the long arm of the X chromosome.

The earliest manifestations of fragile X syndrome involve developmental delay, including delayed attainment of motor and language milestones. Mild to moderate intellectual disability is common. Classic physical features in fragile X syndrome include **macrocephaly**, a **long narrow face**, and a **prominent forehead**, **jaw**, **chin**, and **ears**. **Macroorchidism** (testicular enlargement) is also a key finding. All examination findings tend to be subtle during infancy and become most noticeable after puberty.

(Choice A) Cardinal features of Marfan syndrome are lens dislocation (ectopia lentis) and aortic root dilation. Other common abnormalities include arachnodactyly, scoliosis, and mitral valve prolapse. Cognition and chromosomal studies are typically normal in these patients.

(Choice C) Down syndrome is the most common genetic cause of intellectual disability. Classic findings include short neck, low-set ears, epicanthic folds, and slanted palpebral fissures. Cytogenetic studies usually show a karyotype with 47 chromosomes, including 3 copies of chromosome 21.

(Choice D) Fetal alcohol syndrome is characterized by facial dysmorphisms (short palpebral fissures, indistinct philtrum, thin vermillion border), poor growth, and neurobehavioral problems.

(Choice E) Klinefelter syndrome (47,XXY) presents with tall stature, gynecomastia, and small, firm testes. Decreased testosterone secretion by fibrotic testes causes oligospermia and infertility.

Educational objective:
Fragile X syndrome, an X-linked disorder, is the most common cause of inherited intellectual disability. The pathogenesis involves an unstable expansion of trinucleotide repeats (CGG) in the fragile X mental retardation 1 (*FMR1*) gene. Key physical findings include dysmorphic facial features (eg, large jaw, protruding ears, long face) and macroorchidism.

References

- Fragile X syndrome: a review of associated medical problems

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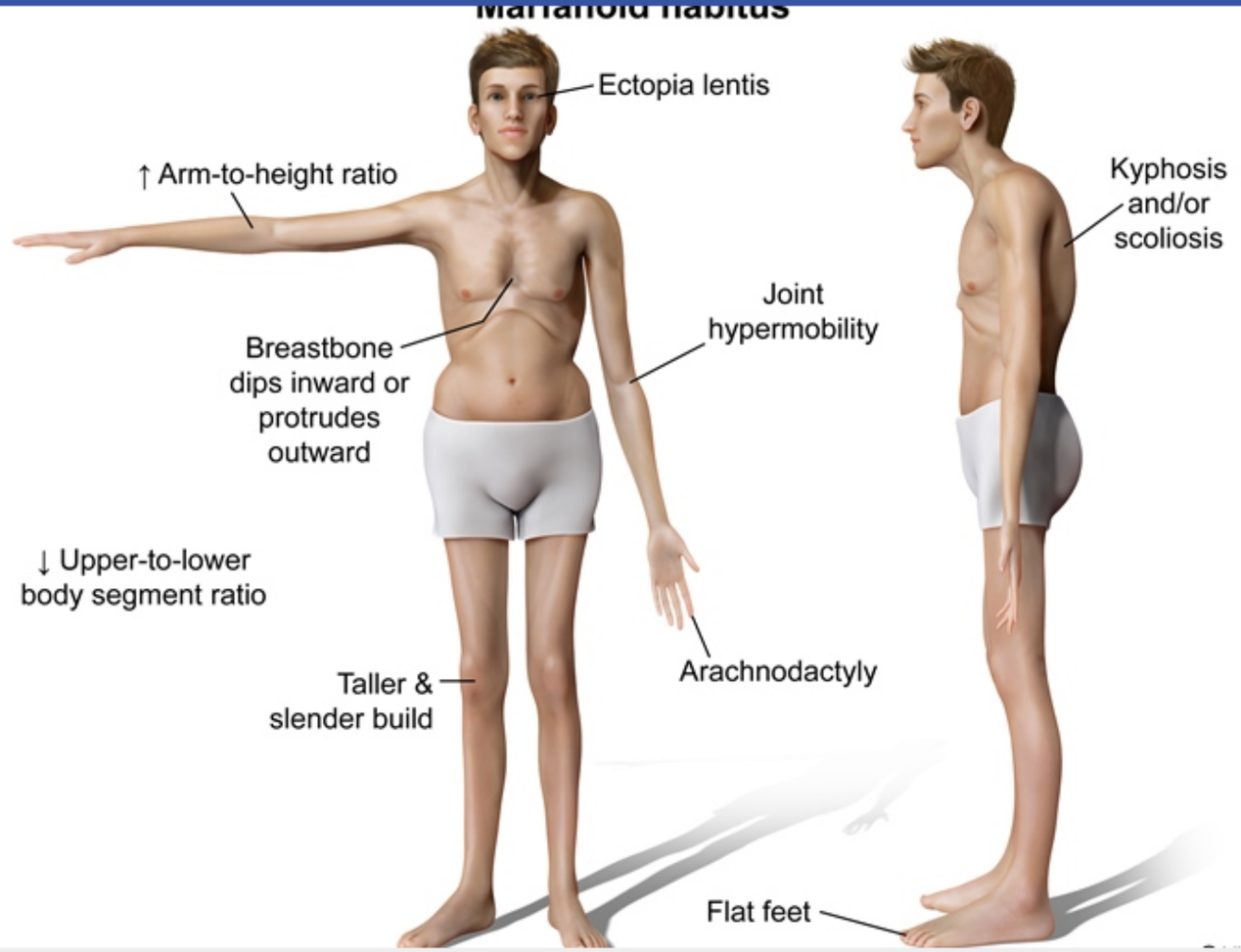

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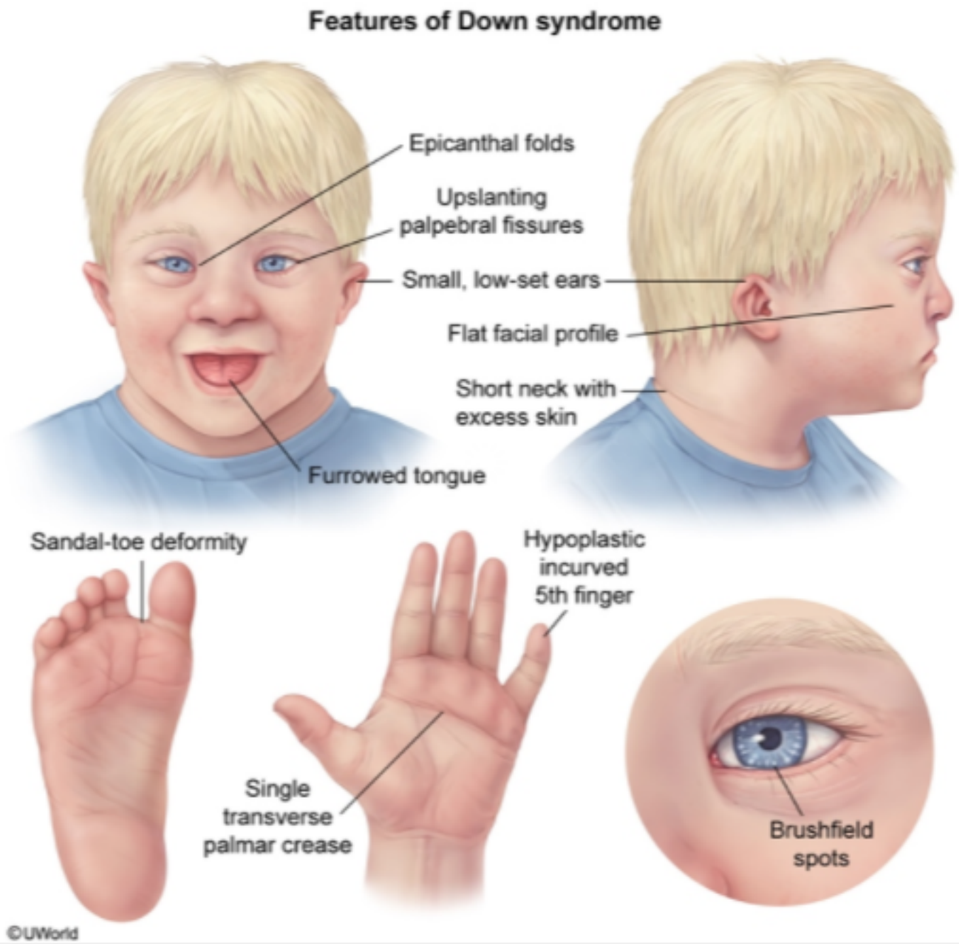

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Fragile X syndrome: a review of associated medical problems

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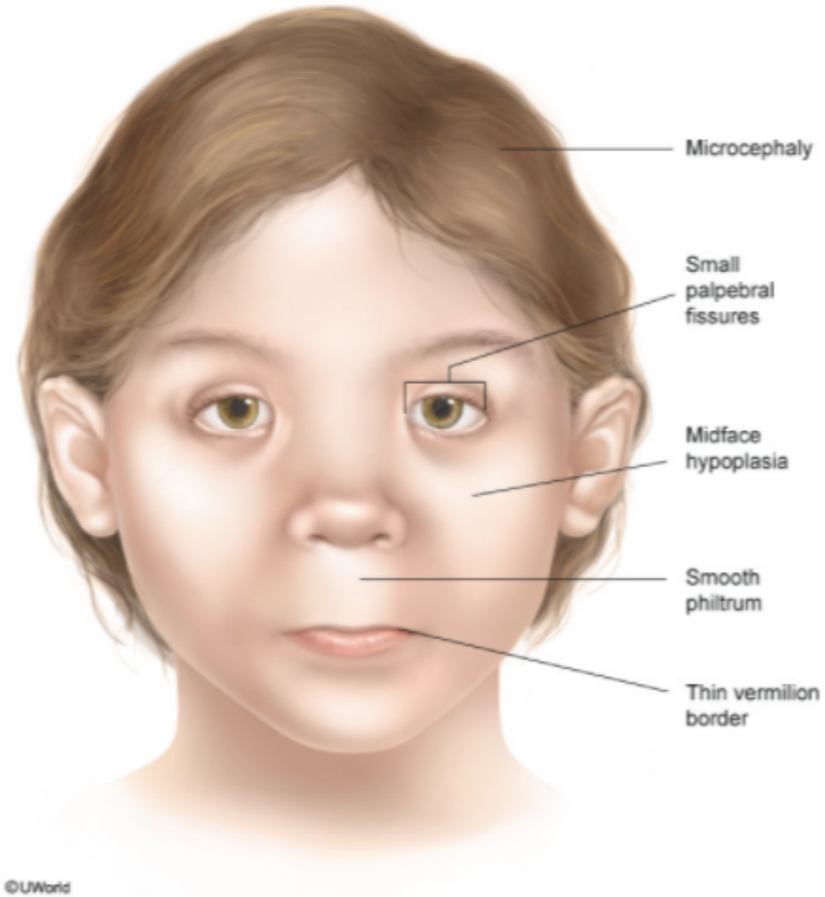
Fetal alcohol syndrome



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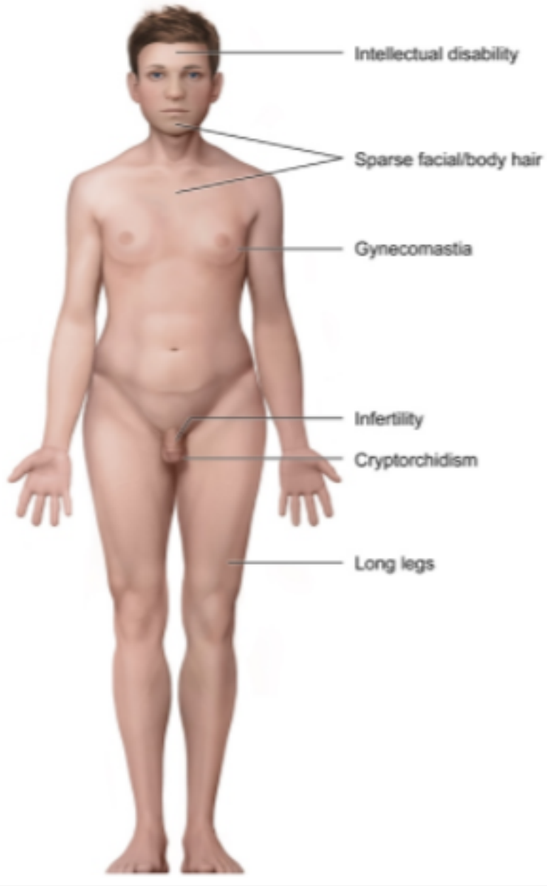
Klinefelter syndrome (47,XXY)



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- Fragile X syndrome: a review of associated medical problems

A 45-year-old man comes to the physician because of involuntary movements and behavioral disturbance. He has frequent, jerky, irregular movements of his upper extremities that have progressively worsened over the past month. His family and friends also say that he has become increasingly irritable over the past year. Genetic testing shows a mutation affecting the huntingtin protein that causes transcriptional repression of a number of other genes. Which of the following mechanisms is most likely responsible for the decreased gene expression seen in this patient?

- A. DNA hypomethylation
- B. Histone deacetylation
- C. Loss of normal huntingtin protein function
- D. Mutation of homeodomain genes
- E. Thymidine dimerization

Submit

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- A. DNA hypomethylation (12%)
- ✓ B. Histone deacetylation (42%)
- C. Loss of normal huntingtin protein function (34%)
- D. Mutation of homeodomain genes (7%)
- E. Thymidine dimerization (2%)

Omitted
Correct answer
B

42%
Answered correctly

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04/25/2020
Last Updated

Explanation

Transcriptional repression in Huntington disease

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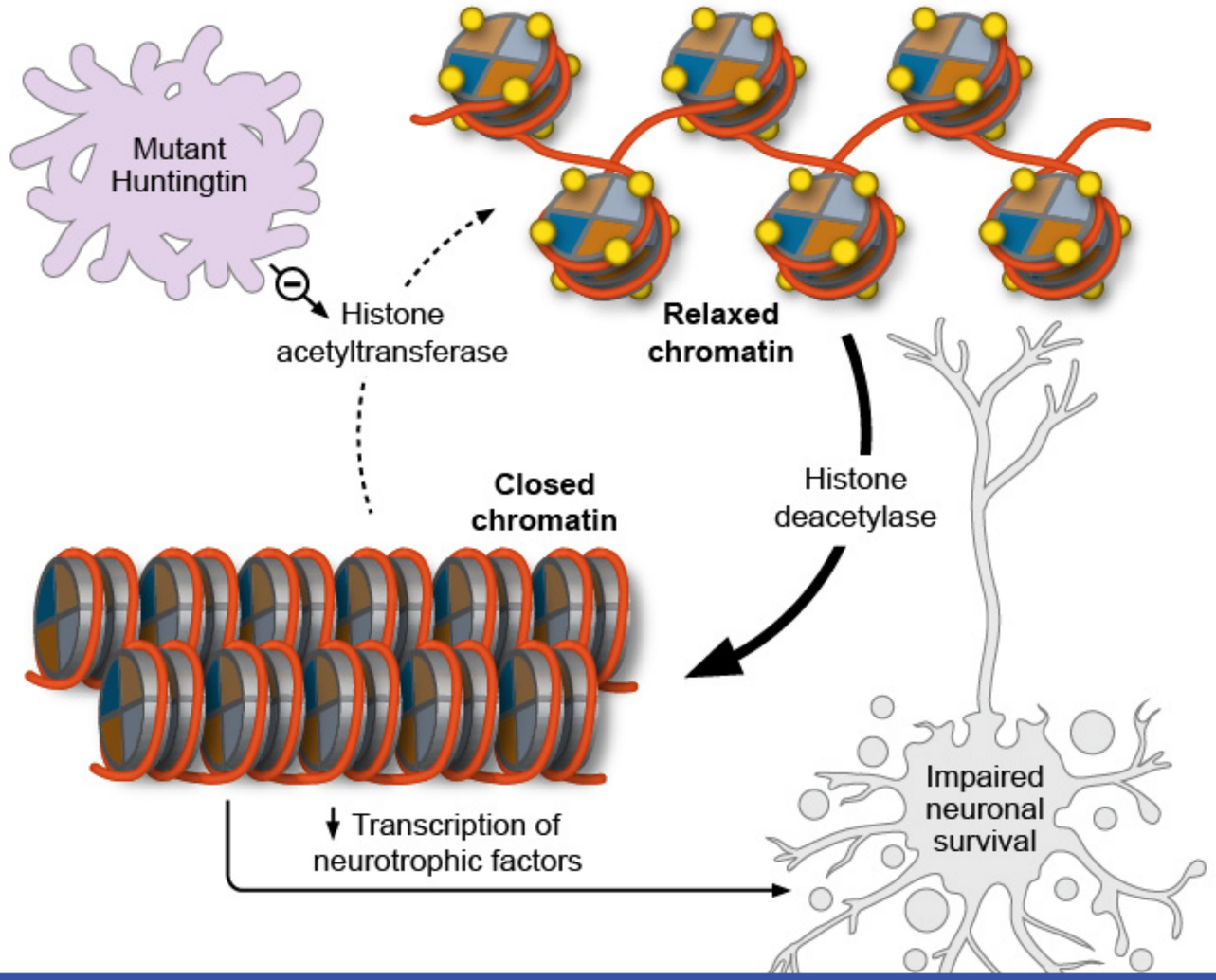
Transcriptional repression in Huntington disease



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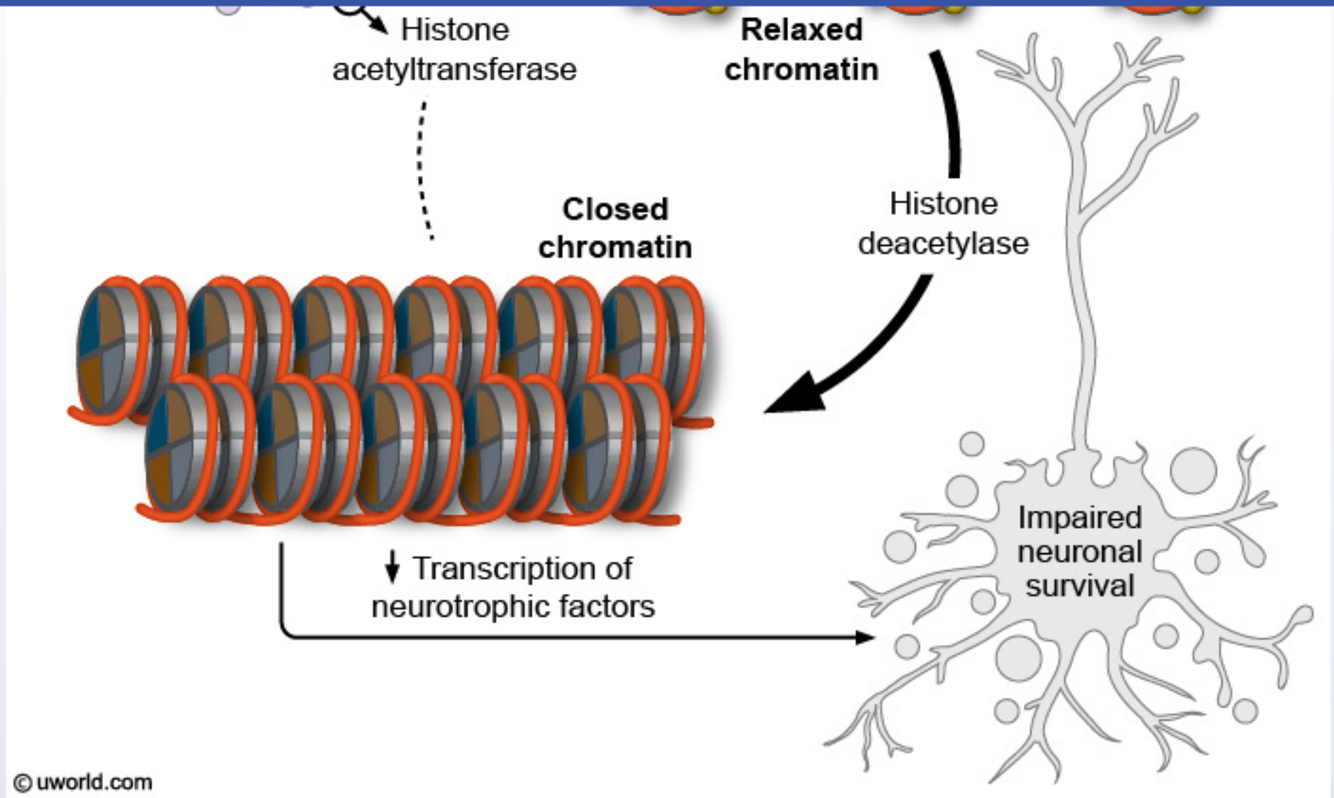

Huntington disease is an autosomal-dominant neurodegenerative disease caused by an increase in the number of **CAG trinucleotide repeats** in the gene that codes for the **huntingtin** protein. Expansion of the protein's polyglutamine region results in a **gain-of-function** that leads to pathological interaction with other proteins, including various transcription factors.

Transcriptional repression (silencing) is one of the mechanisms by which mutated huntingtin is thought to cause disease. Regulation of transcription occurs in part due to the presence of histones, small proteins that complex with DNA to help compact the strands. Histones can undergo a variety of modifications (eg, methylation, acetylation, phosphorylation) that affect the accessibility of the genome for transcription. Acetylation of histones weakens the DNA-histone bond and makes DNA segments more accessible for transcription factors and RNA polymerases, enhancing gene transcription. In Huntington disease, abnormal huntingtin causes increased **histone deacetylation**, silencing the

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(Choice A) DNA methylation is an epigenetic modification that acts to inhibit gene transcription. Hypermethylation of the promotor region of a gene results in transcriptional silencing; hypomethylation improves gene expression.

(Choice C) The manifestations of Huntington disease are caused by a deleterious gain of function mutation. Although the normal function of huntingtin is not completely understood, it is known to play a critical role in embryonic development; loss of huntingtin results in embryonic death.

(Choice D) Homeodomain (homeobox) genes are critical for the sequential development of organs and tissues along the body axis during embryogenesis. Mutations affecting these genes cause alterations in body structure, leading to congenital malformations or spontaneous abortion.

(Choice E) Thymidine dimerization is a mechanism of DNA damage induced by ultraviolet radiation.

Educational objective:
Hypo-acetylated histones bind tightly to DNA and prevent transcription of genes in their associated regions. Alteration of gene expression in Huntington disease occurs in part due to deacetylation of histones. This prevents the transcription of certain genes that code for neurotrophic factors, contributing to neuronal cell death.

References

Acetylation of histones weakens the DNA-histone bond and makes DNA segments more accessible for transcription factors and RNA polymerases, enhancing gene transcription. In Huntington disease, abnormal huntingtin causes increased **histone deacetylation**, silencing the genes necessary for neuronal survival. As a result, one of the treatment options under investigation includes histone deacetylase inhibitors that help upregulate survival genes.

(Choice A) DNA methylation is an epigenetic modification that acts to inhibit gene transcription. Hypermethylation of the promotor region of a gene results in transcriptional silencing; hypomethylation improves gene expression.

(Choice C) The manifestations of Huntington disease are caused by a deleterious gain of function mutation. Although the normal function of huntingtin is not completely understood, it is known to play a critical role in embryonic development; loss of huntingtin results in embryonic death.

(Choice D) Homeodomain (homeobox) genes are critical for the sequential development of organs and tissues along the body axis during embryogenesis. Mutations affecting these genes cause alterations in body structure, leading to congenital malformations or spontaneous abortion.

(Choice E) Thymidine dimerization is a mechanism of DNA damage induced by ultraviolet radiation.

Educational objective:
Hypo-acetylated histones bind tightly to DNA and prevent transcription of genes in their associated regions. Alteration of gene expression in Huntington disease occurs in part due to deacetylation of histones. This prevents the transcription of certain genes that code for neurotrophic factors, contributing to neuronal cell death.

References

- Mechanisms of disease: histone modifications in Huntington's disease.
- Epigenetic mechanisms of neurodegeneration in Huntington's disease.

Genetics	Nervous System	Huntington disease
Subject	System	Topic

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A 14-year-old boy with chronic anemia is being evaluated after experiencing several episodes of chest, back, and extremity pain. Peripheral blood smear shows sickle-shaped red cells. Genetic testing reveals that the patient is homozygous for a point mutation in the beta-globin gene, resulting in a glutamic acid to valine substitution at position 6. Sequencing of the beta-globin gene would most likely reveal which of the following changes? (The genetic code is shown in the figure below.)

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First position (5' end)	Second position				Third position (3' end)
	U/T	C	A	G	
U/T	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr Stop Stop	Cys Cys Stop Trp	U/T C A G
C	Leu Leu Leu	Pro Pro Pro	His His Gln	Arg Arg Arg	U/T C A

Exhibit Display

First position (5' end)	Second position				Third position (3' end)
	U/T	C	A	G	
U/T	Phe Phe Leu Leu	Ser Ser Ser Ser	Tyr Tyr Stop Stop	Cys Cys Stop Trp	U/T C A G
C	Leu Leu Leu Leu	Pro Pro Pro Pro	His His Gln Gln	Arg Arg Arg Arg	U/T C A G
A	Ile Ile Ile Met	Thr Thr Thr Thr	Asn Asn Lys Lys	Ser Ser Arg Arg	U/T C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U/T C A G

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A	Ile Ile Met	Thr Thr Thr	Asn Lys Lys	Ser Arg Arg	C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U/T C A G

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- A. CAA → GTT
- B. CAT → CTT
- C. TTA → CTA
- D. GAA → GUA
- E. GAG → GTG
- F. GTA → GAA

Submit

A	Ile Ile Met	Thr Thr Thr	Asn Lys Lys	Ser Arg Arg	C A G
G	Val Val Val Val	Ala Ala Ala Ala	Asp Asp Glu Glu	Gly Gly Gly Gly	U/T C A G

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A. CAA → GTT (4%)
B. CAT → CTT (1%)
C. TTA → CTA (1%)
D. GAA → GUA (25%)
✓ E. GAG → GTG (61%)
F. GTA → GAA (5%)

Omitted
Correct answer

61%
Answered correctly

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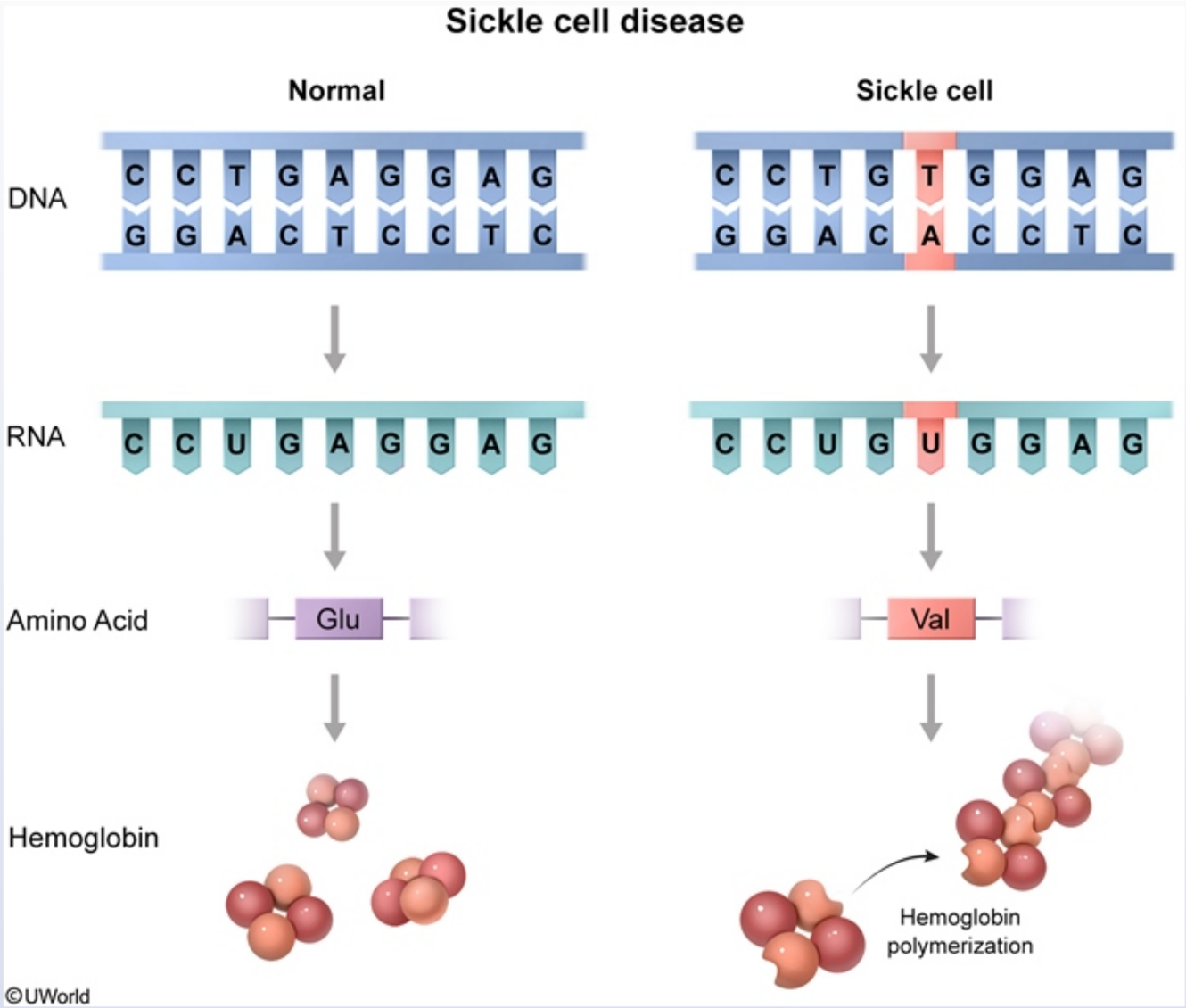

This patient has **sickle cell disease** (SCD), an autosomal recessive hematologic disorder resulting in hemoglobin molecules that polymerize

This patient has **sickle cell disease** (SCD), an autosomal recessive hematologic disorder resulting in hemoglobin molecules that polymerize during times of hypoxic stress. SCD results from a DNA point mutation in the coding region of the hemoglobin beta-globin chain. This single nucleotide substitution is a missense mutation that causes a **glutamic acid to valine substitution at position 6** during protein translation. The genetic code figure shows that 2 distinct nucleotide combinations code for glutamic acid, GAG and GAA. In addition, only 2 possible single nucleotide substitutions could occur in DNA that result in glutamic acid being replaced by valine, GAA → GTA and **GAG → GTG**.

(Choices A, B, and F) Examples of missense mutations include glutamine (CAA) substitution by valine (GTT), histidine (CAT) substitution by leucine (CTT), and valine (GTA) substitution by glutamic acid (GAA). However, they are unrelated to SCD.

(Choice C) This substitution results in a silent mutation as both TTA and CTA code for leucine.

(Choice D) A codon change from GAA to GUA also results in glutamic acid being replaced by valine. However, the pyrimidine base uracil occurs only in RNA (not DNA), so it would only be present in the mRNA transcript that codes for the beta-globin protein and not in the beta-globin gene itself.

Educational objective:
Sickle cell disease is the result of a missense mutation that causes valine to replace glutamic acid at position 6 in the hemoglobin beta-globin chain. RNA contains the pyrimidine base uracil, whereas DNA contains the base thymidine.

References

- Sickle cell pathophysiology

Genetics	Hematology & Oncology	Sickle cell
Subject	System	Topic

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Hemoglobin

Exhibit Display

Types of DNA mutations	
Silent	Base substitution codes for same amino acid
Missense	Base substitution codes for different amino acid
Conservative	Base substitution codes for different amino acid with similar chemical structure
Nonsense	Base substitution introduces premature stop codon
Nonstop	Base substitution within stop codon results in continued translation
Splice site	Mutation at splice site alters intron removal from pre-mRNA
Frameshift	Deletion/insertion of bases causes downstream misreading

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A 35-year-old woman, gravida 1, para 0, comes to the office to discuss abnormal laboratory results. The patient is at 18 weeks gestation based on her last menstrual period. She drank wine during the first trimester, as she initially did not realize she was pregnant. The patient is otherwise healthy with no medical problems. She takes prenatal vitamins and no other medications. Her immunizations are up-to-date. Results of the quadruple screen performed yesterday are as follows:

Maternal serum α-fetoprotein	Low
Unconjugated estriol	Low
β-hCG	High
Inhibin A	High

An ultrasound is scheduled to confirm the patient's gestational age and evaluate for fetal anomalies. Which of the following conditions is the most likely cause of this patient's analyte pattern?

A. Fetal alcohol syndrome
B. Gastroschisis
C. Myelomeningocele
D. Omphalocele
E. Trisomy 21

Submit

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Unconjugated estriol	Low
β-hCG	High
Inhibin A	High

An ultrasound is scheduled to confirm the patient's gestational age and evaluate for fetal anomalies. Which of the following conditions is the most likely cause of this patient's analyte pattern?

A. Fetal alcohol syndrome (13%)
B. Gastroschisis (1%)
C. Myelomeningocele (4%)
D. Omphalocele (1%)
✓ E. Trisomy 21 (78%)

Omitted
Correct answer
E

78%
Answered correctly

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Time Spent

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Last Updated

Maternal serum alpha-fetoprotein screening	
↑ MSAFP	↓ MSAFP
• Open neural tube defects (eg, anencephaly, open spina bifida) • Ventral wall defects (eg, omphalocele, gastroschisis) • Multiple gestation	• Aneuploidies (eg, trisomy 18 & 21)

MSAFP = maternal serum alpha-fetoprotein.

Down syndrome (DS) is the most common chromosomal abnormality and most common genetic cause of **intellectual disability**. Risk factors include **advanced maternal age (age ≥35)** and a parent with a Robertsonian translocation. DS can be screened and diagnosed prenatally. One common option for screening during the second trimester is the **quadruple screen** at 15-18 weeks gestation. **Low maternal serum α-fetoprotein (AFP) and unconjugated estriol** levels are associated with DS and correlate with decreased fetal levels (possibly due to suboptimal fetal tissue function). In addition, **increased β-hCG and inhibin A** are secreted from the placenta, possibly due to compensatory placental hyperfunction. The diagnosis is confirmed by karyotyping fetal cells in the amniotic fluid (amniocentesis).

The vast majority of patients with DS have trisomy 21 from meiotic nondisjunction, specifically, failure of chromosome 21 to divide during meiosis. Chromosome 21 nondisjunction occurs during **oogenesis** and is significantly associated with advanced maternal age; it is not seen in spermatogenesis or in post-zygotic mitotic errors. DS can also result from an **unbalanced Robertsonian translocation**, during which the entire long arm of one chromosome 21 is translocated to the long arm of an acrocentric chromosome (ie, chromosome 14). These individuals have 46 chromosomes; however, one chromosome 14 is comprised of the long arms of both chromosomes 14 and 21.

(Choice A) Abstinence from alcohol is advised for all pregnant women as the amount that can cause teratogenicity is not known. However, the quadruple test is not used to screen for fetal alcohol syndrome.

(Choices B, C, and D) Omphalocele and gastroschisis cause increased AFP levels in maternal serum and amniotic fluid. High AFP is also associated with multiple gestation and open neural tube defects (eg, myelomeningocele). Neural tube defects are also associated with increased acetylcholinesterase levels in amniotic fluid.

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Educational objective:
Down syndrome is the most common chromosomal anomaly. It is associated with low levels of maternal serum α-fetoprotein and estriol and increased levels of β-hCG and inhibin A. Elevated α-fetoprotein levels are seen in multiple gestation, open neural tube defects, and abdominal wall defects.

References

- Influence of second-trimester ultrasound markers for Down syndrome in pregnant women of advanced maternal age.
- The quadruple test for Down syndrome screening in pregnant women of advanced maternal age.

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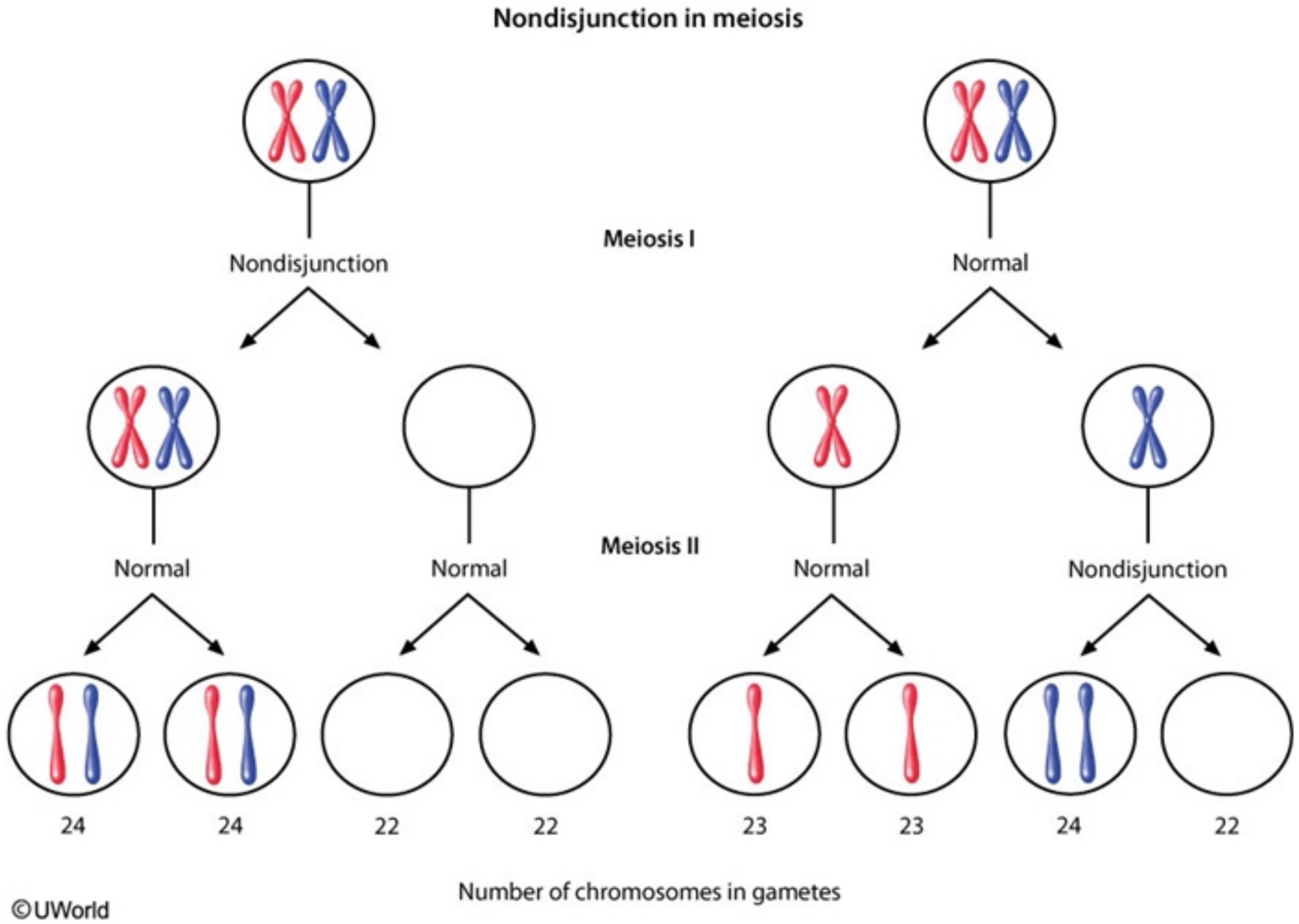

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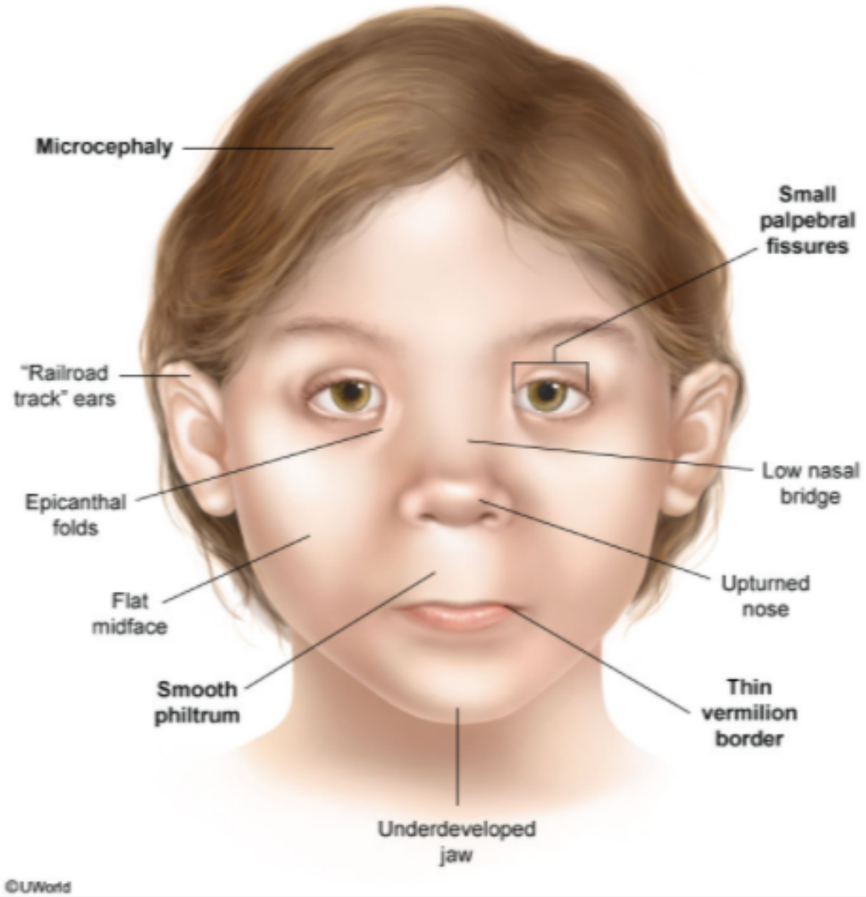
MSAFP maternal serum alpha fetoprotein.

Exhibit Display

Fetal alcohol syndrome



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The quadruple test for Down syndrome screening in pregnant women of advanced maternal age.

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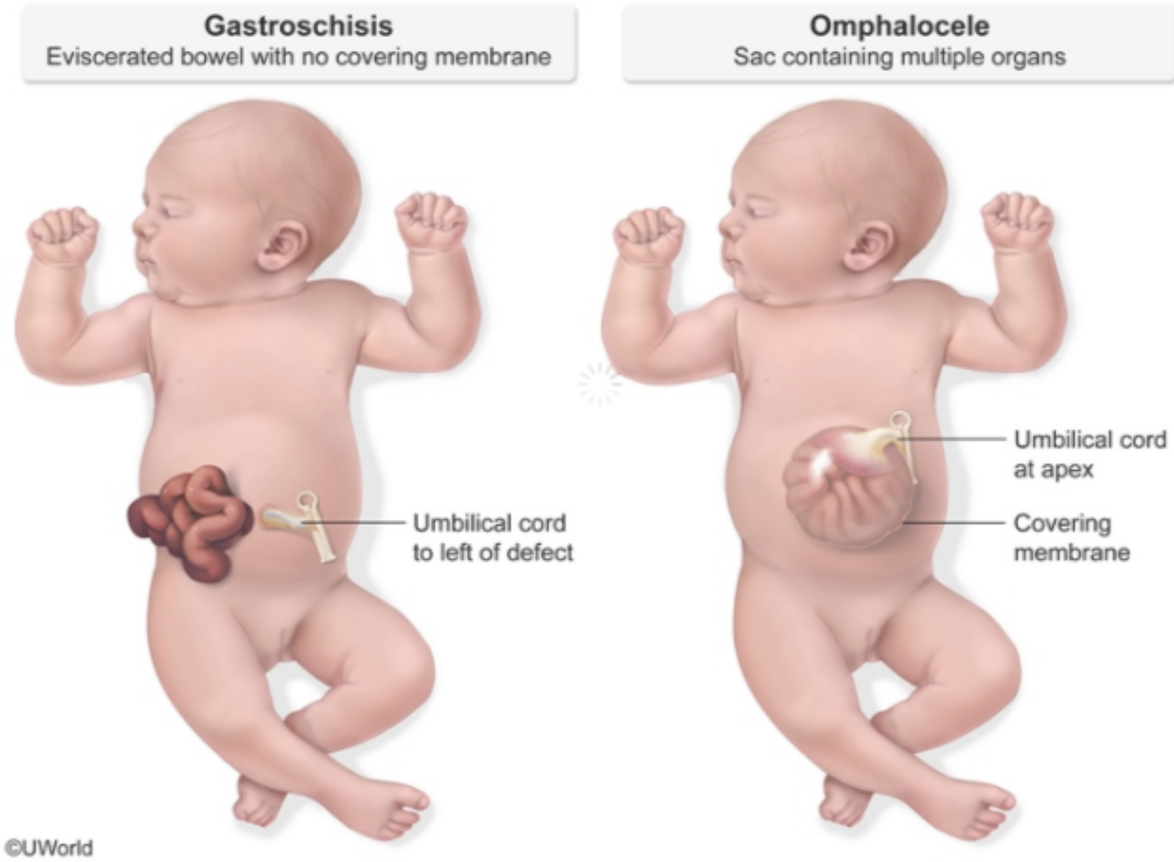
MSAFP maternal serum alpha fetoprotein.

Exhibit Display

Gastroschisis vs. omphalocele



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The quadruple test for Down syndrome screening in pregnant women of advanced maternal age.

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A healthy, nulliparous 29-year-old woman with regular 28-day cycles comes to the office for a fertility evaluation. Over the past year, she and her 30-year-old husband have been trying to conceive. Her only medications are prenatal vitamins. She tracks her periods, cervical mucus, basal temperature, and intercourse with a smartphone app. The couple has intercourse every other day from cycle day 8 through the LH surge. The patient's urine pregnancy test is positive. The oocyte was most likely arrested in which of the following stages of meiosis immediately prior to fertilization?

A. Metaphase of meiosis I
B. Metaphase of meiosis II
C. Prophase of meiosis I
D. Prophase of meiosis II
E. Telophase of meiosis I
F. Telophase of meiosis II

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- A. Metaphase of meiosis I (6%)
- ✓ B. Metaphase of meiosis II (62%)
- C. Prophase of meiosis I (11%)
- D. Prophase of meiosis II (16%)
- E. Telophase of meiosis I (1%)
- F. Telophase of meiosis II (1%)

Omitted
Correct answer
B

62%
Answered correctly

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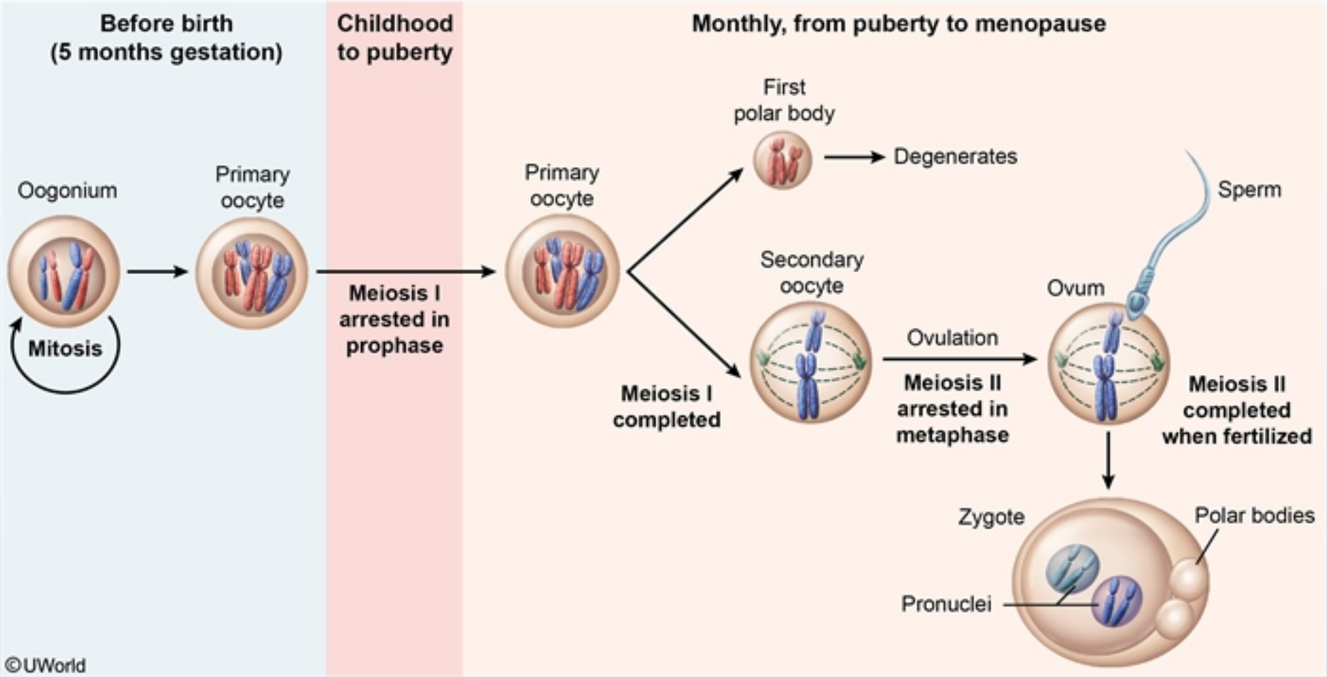
Last Updated

Explanation

Before birth (5 months gestation)	Childhood to puberty	Monthly, from puberty to menopause
		First polar body



Female gametogenesis begins in utero at approximately 4 weeks gestation when primordial germ cells migrate from the yolk sac region to the developing gonadal region. These germ cells then differentiate into oogonia and multiply by mitosis before beginning meiosis I. Now called **primary oocytes**, these cells arrest in **prophase of meiosis I (Choice C)** and remain there until ovulation. The chromosome pairs are arranged in a tetrad during this phase, and their proximity allows for genetic recombination. The full complement of oocytes is developed by 5 months gestation and then degenerates during the woman's lifetime until depleted at menopause.

At puberty, ovulatory cycles begin and the female is capable of reproduction. During each menstrual cycle, FSH stimulation followed by an LH surge causes some oocytes to resume meiosis I. Telophase I **(Choice E)** is the last phase of meiosis I and yields secondary oocytes and polar bodies. The secondary oocyte begins meiosis II (the polar body degenerates) but halts in metaphase II. Approximately 36 hours after LH levels begin to rise, a secondary oocyte is released from the ovarian follicle. The secondary oocyte remains frozen in **metaphase II until fertilization**

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(Choice A) Metaphase of meiosis I differs from metaphase of meiosis II and mitosis, as the spindles are not preparing to split the centromeres. Instead, the tetrads are lined up along the metaphase plate, and during anaphase the homologs separate from each other with the centromeres intact.

(Choice D) Prophase of meiosis II is unique as it does not immediately follow a period of DNA synthesis; DNA was duplicated prior to prophase of meiosis I.

Educational objective:
Primary oocytes are completely developed in female embryos by the fifth month of gestation, at which point they are arrested in prophase of meiosis I. Normal menstrual cycle hormones stimulate the primary oocyte to resume differentiation. Prior to fertilization, secondary oocytes are arrested in metaphase of meiosis II.

References

- Oocyte maturation: gamete-somatic cells interactions, meiotic resumption, cytoskeletal dynamics and cytoplasmic reorganization.

Genetics | Pregnancy, Childbirth & Puerperium | Embryologic derivatives

Female gametogenesis begins in utero at approximately 4 weeks gestation when primordial germ cells migrate from the yolk sac region to the

Exhibit Display

Gametogenesis

Female	Male	Cell cycle stage	# homologs (n)	# chromatids (c)	
Oogonia	Spermatagonia	G0	2n (46)	2c	
Primary oocyte	Primary spermatocyte	Prophase MI	2n (46)	4c	
Secondary oocyte	Secondary spermatocyte	Metaphase MII	1n (23)	2c	
Mature ovum	Spermatid	Telophase MII	1n (23)	1c	

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A 12-year-old Caucasian male with history of seizure disorder experiences several stroke-like episodes with residual neurological deficit. He also suffers from muscle weakness. Blood tests show increased serum lactate levels both post-exercise and at rest. This patient's condition is known to be maternally inherited. This patient's sister is also affected by the same disorder, but she displays very few symptoms. Which of the following is the most likely explanation for the variability in clinical presentation between the patient and his sister?

A. Genetic imprinting

B. Heteroplasmy

C. Anticipation

D. Low expression variability

E. Female sparing

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A. Genetic imprinting (8%)
✓ B. Heteroplasmy (60%)
C. Anticipation (2%)
D. Low expression variability (15%)
E. Female sparing (12%)

Omitted
Correct answer
B

60%
Answered correctly

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Time Spent

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Last Updated

Explanation

Mitochondria have a small amount of their own DNA, called mitochondrial DNA (mtDNA), which can have deletions and point mutations just like regular DNA. Mitochondrial disorders (mutations in mtDNA) are unique in that they are exclusively inherited from one's mother. Recall that the ovum is relatively large and has many copies of mtDNA; whereas, the few copies of mtDNA present in sperm are lost during fertilization.

Mitochondrial diseases affect both male and female offspring with equal frequency (100%), but there are variable degrees of severity. This variability occurs because, during mitosis, mitochondria are randomly distributed between daughter cells. As a result, some cells contain

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Mitochondrial diseases affect both male and female offspring with equal frequency (100%), but there are variable degrees of severity. This variability occurs because, during mitosis, mitochondria are randomly distributed between daughter cells. As a result, some cells contain mitochondria with mostly damaged mtDNA, while some contain mostly normal mitochondrial genomes. This mixture of two types of genetic material is called **heteroplasmy** and is responsible for the clinical variability of mitochondrial diseases. The following mitochondrial syndromes are important:

1. *Leber hereditary optic neuropathy* leads to bilateral vision loss.
2. *Myoclonic epilepsy with ragged-red fibers*: myoclonic seizures and myopathy associated with exercise. Skeletal muscle biopsy shows irregularly shaped muscle fibers (ragged red fibers).
3. *Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)*. The clinical presentation of MELAS is described in this vignette.

(Choice A) Genetic imprinting is a selective inactivation of paternal or maternal alleles. This phenomenon explains the differences in clinical presentation between Prader-Willi and Angelman syndromes.

(Choice C) Anticipation refers to the increase in severity of genetic disorders in subsequent generations. Anticipation is often seen in diseases involving an increased number of trinucleotide repeats, such as Huntington disease and Fragile X syndrome.

(Choice D) Variable expressivity refers to the differences in severity of autosomal dominant disorders. For example, a patient with Marfan syndrome may have only tall stature, while another patient with the same genetic defect will have tall stature, aortic root dilation, and lens dislocation. Variable expressivity is not a feature of mitochondrial diseases.

(Choice E) Female sparing is not characteristic of mitochondrial disorders. Both males and females are equally affected in mitochondrial disorders.

Educational Objective:

are important:

1. *Leber hereditary optic neuropathy* leads to bilateral vision loss.
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(Choice E) Female sparing is not characteristic of mitochondrial disorders. Both males and females are equally affected in mitochondrial disorders.

Educational Objective:
Mitochondrial diseases are characterized by exclusively-maternal inheritance. The variable severity of these diseases is explained by the random distribution of normal and mutated mitochondria between daughter cells during mitosis; as a result, some cells may have completely healthy mitochondria, while other cells contain mitochondria affected by genetic mutation (heteroplasmy). MELAS is a mitochondrial syndrome.

Genetics	Nervous System	Mitochondrial disorders
Subject	System	Topic

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An infant born to a 26-year-old woman is evaluated shortly after delivery. Birth weight and length are at the 10th and 15th percentiles, respectively. Vital signs are normal. Physical examination shows a protruding tongue, excessive skin at the nape of the neck, and upslanting palpebral fissures. The startle reflex is symmetric and weak. Cardiac auscultation reveals a harsh, III/VI systolic murmur heard best over the lower left sternal border. The patient has normal external female genitalia. Review of maternal medical records shows a past history of 2 spontaneous abortions in the last 3 years. Echocardiography confirms the presence of a ventricular septal defect. Which of the following karyotypes is most likely to be found in this infant?

A. 45,XO

B. 46,XX, del(22)(q11)

C. 46,XX, t(9;22)

D. 46,XX, t(14;21)

E. 47,XX, +18

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An infant born to a 26-year-old woman is evaluated shortly after delivery. Birth weight and length are at the 10th and 15th percentiles, respectively. Vital signs are normal. Physical examination shows a protruding tongue, excessive skin at the nape of the neck, and upslanting palpebral fissures. The startle reflex is symmetric and weak. Cardiac auscultation reveals a harsh, III/VI systolic murmur heard best over the lower left sternal border. The patient has normal external female genitalia. Review of maternal medical records shows a past history of 2 spontaneous abortions in the last 3 years. Echocardiography confirms the presence of a ventricular septal defect. Which of the following karyotypes is most likely to be found in this infant?

- A. 45,XO (29%)
- B. 46,XX, del(22)(q11) (7%)
- C. 46,XX, t(9;22) (1%)
- ✓ D. 46,XX, t(14;21) (45%)
- E. 47,XX, +18 (15%)

Omitted
Correct answer
D

45%
Answered correctly

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Time Spent

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Last Updated

Explanation

Robertsonian translocation

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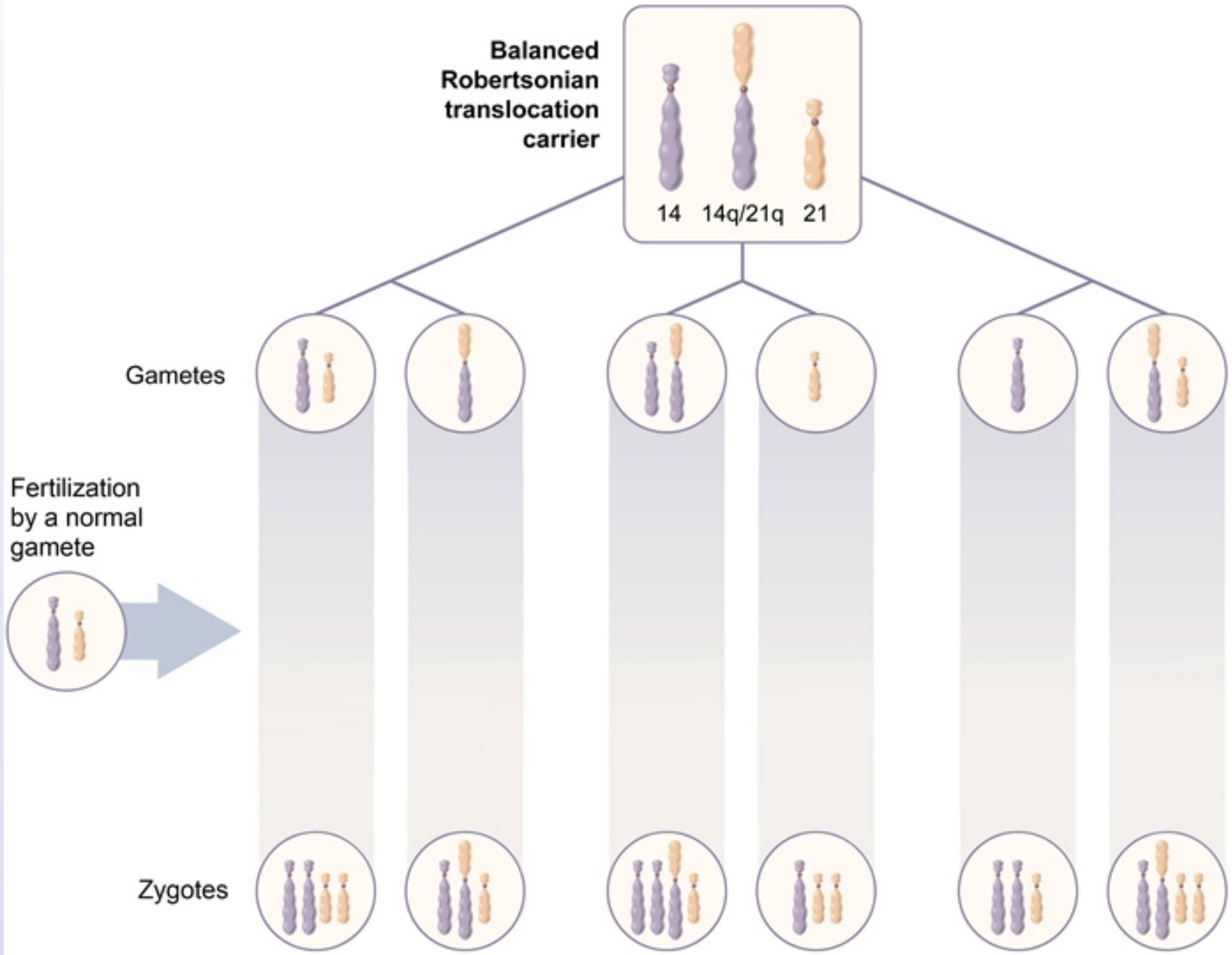
Robertsonian translocation



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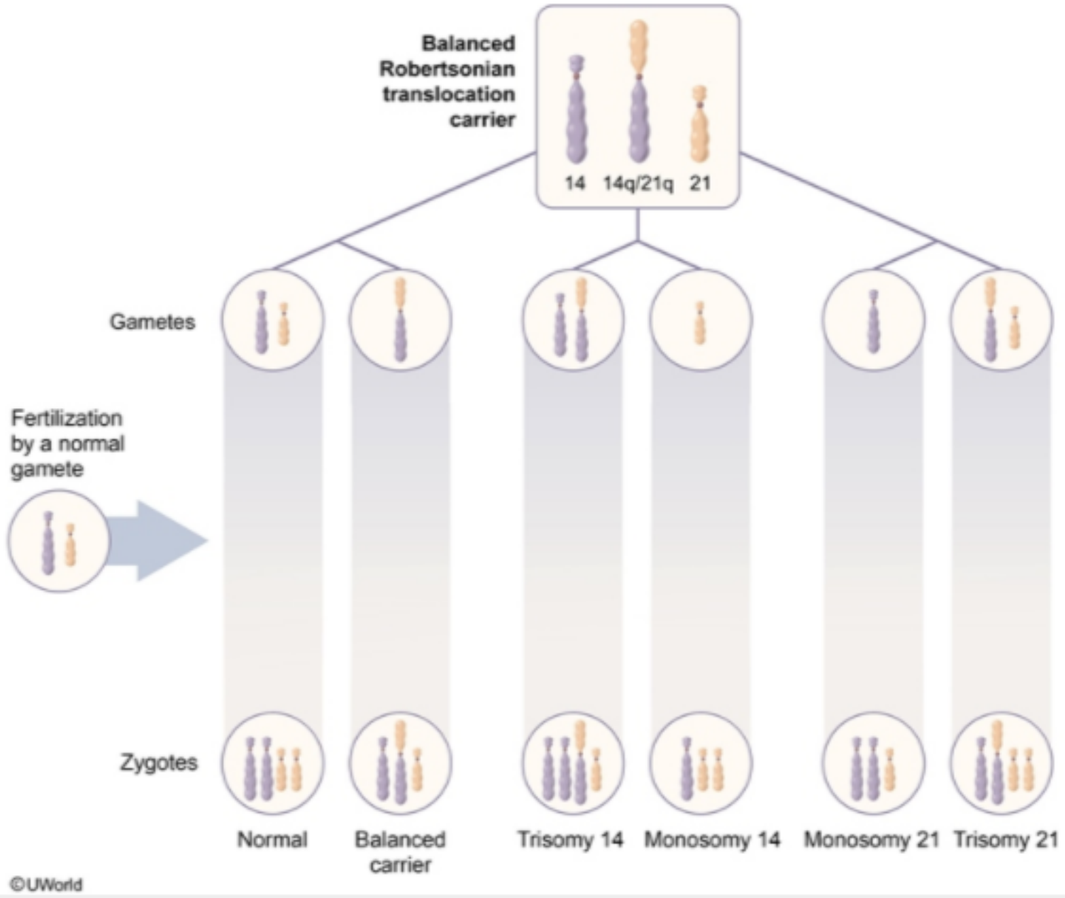
Robertsonian translocation



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carrier

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Down syndrome is most commonly caused by random meiotic nondisjunction, an abnormality that correlates with increasing maternal age and results in 3 complete copies of chromosome 21 (47, XX, +21).

Translocation Down syndrome, which is less common, can be inherited from an unaffected parent with a balanced translocation. Robertsonian translocations occur between 2 acrocentric, nonhomologous chromosomes (eg, 14 and 21). The resultant translocated chromosomes are the fusion of 2 long arms (eg, 14q and 21q [red arrow]) and the fusion of 2 short arms (eg, 14p and 21p); the latter usually contains nonessential genetic material and is lost after several cell divisions. The affected parent is asymptomatic because they have a normal (albeit rearranged) genetic complement. However, when an ovum containing the translocated chromosome and a normal chromosome 21 is fertilized with a sperm containing a normal set of chromosomes (ie, 1 copy of chromosome 21), the resultant fetus has an **unbalanced Robertsonian translocation** with **46 chromosomes** and **3 effective copies** of chromosome 21 [**46,XX, t(14;21)**]. Another possible maternal gamete includes 0 copies of chromosome 21, which increases the rate of **miscarriages** in balanced Robertsonian translocation carriers.

Dysmorphic features of Down syndrome include epicanthal folds, upslanting palpebral fissures, a protruding tongue, and excessive skin at the nape of the neck. Birth weight and length are often below average, and hypotonia and a weak startle (Moro) reflex are characteristic. Cardiac defects are present in >50% of cases.

(Choice A) Turner syndrome (45,XO) presents with low-set ears, a webbed neck, wide-spaced nipples, and cardiac defects (eg, aortic coarctation). Most cases are due to absence of the paternally contributed X chromosome.

(Choice B) DiGeorge syndrome, caused by sporadic 22q11 deletions, presents with hypertelorism, micrognathia, cleft palate, and cardiac defects (eg, interrupted aortic arch, Tetralogy of Fallot).

(Choice C) The Philadelphia chromosome is a balanced translocation between chromosomes 9 and 22 that produces an oncogenic fusion gene (*BCR-ABL*) associated with chronic myelogenous leukemia.

(Choice E) Trisomy 18 (47, XX, +18), or Edwards syndrome, usually arises secondary to meiotic nondisjunction with maternal age ≥35. Findings include dysmorphic facies (eg, micrognathia, low-set ears), clenched hands with overlapping fingers, and hypertonia.

Educational objective:

Unbalanced Robertsonian translocations account for a minority of Down syndrome cases. Karyotyping shows 46 chromosomes with a

carrier

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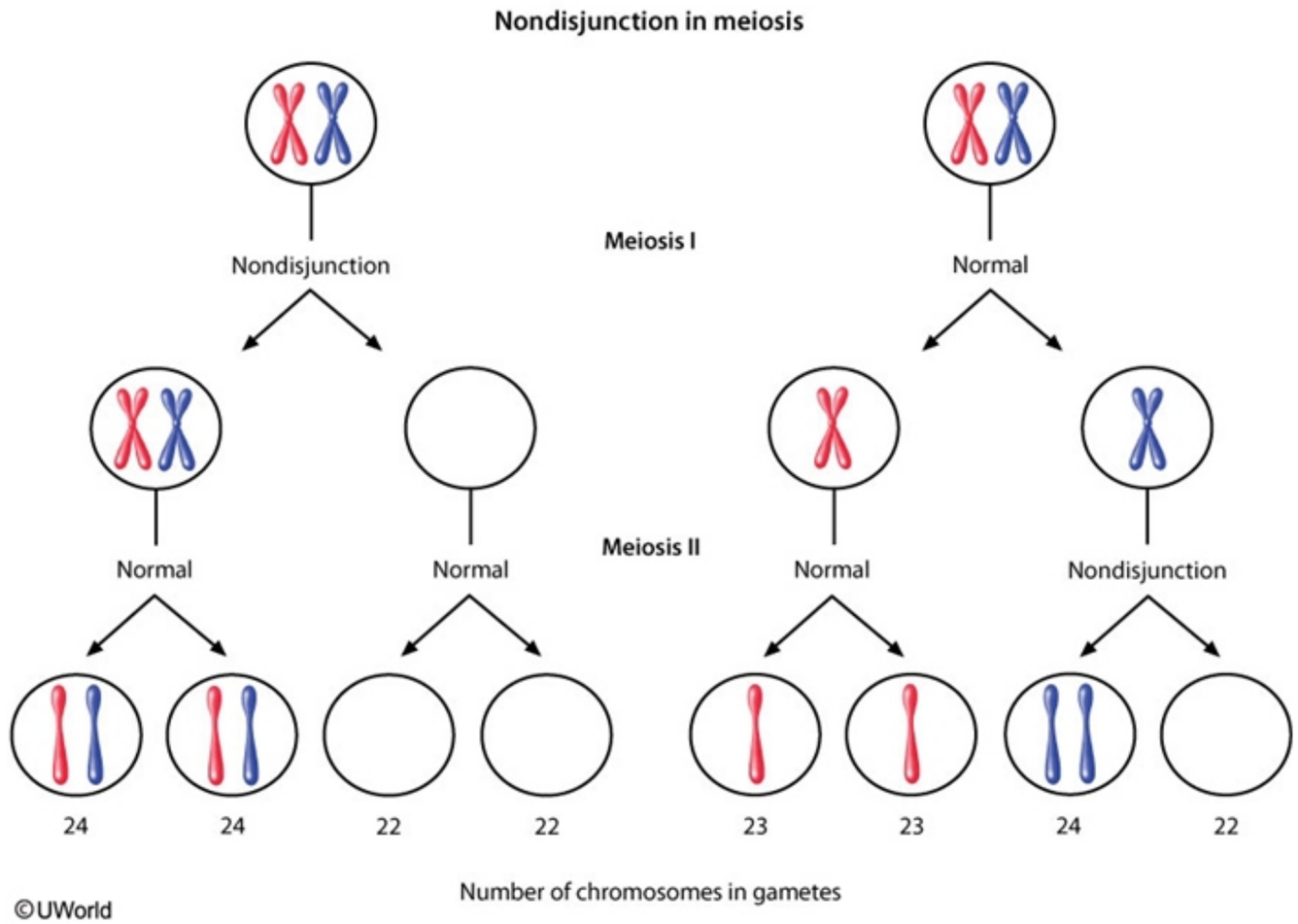

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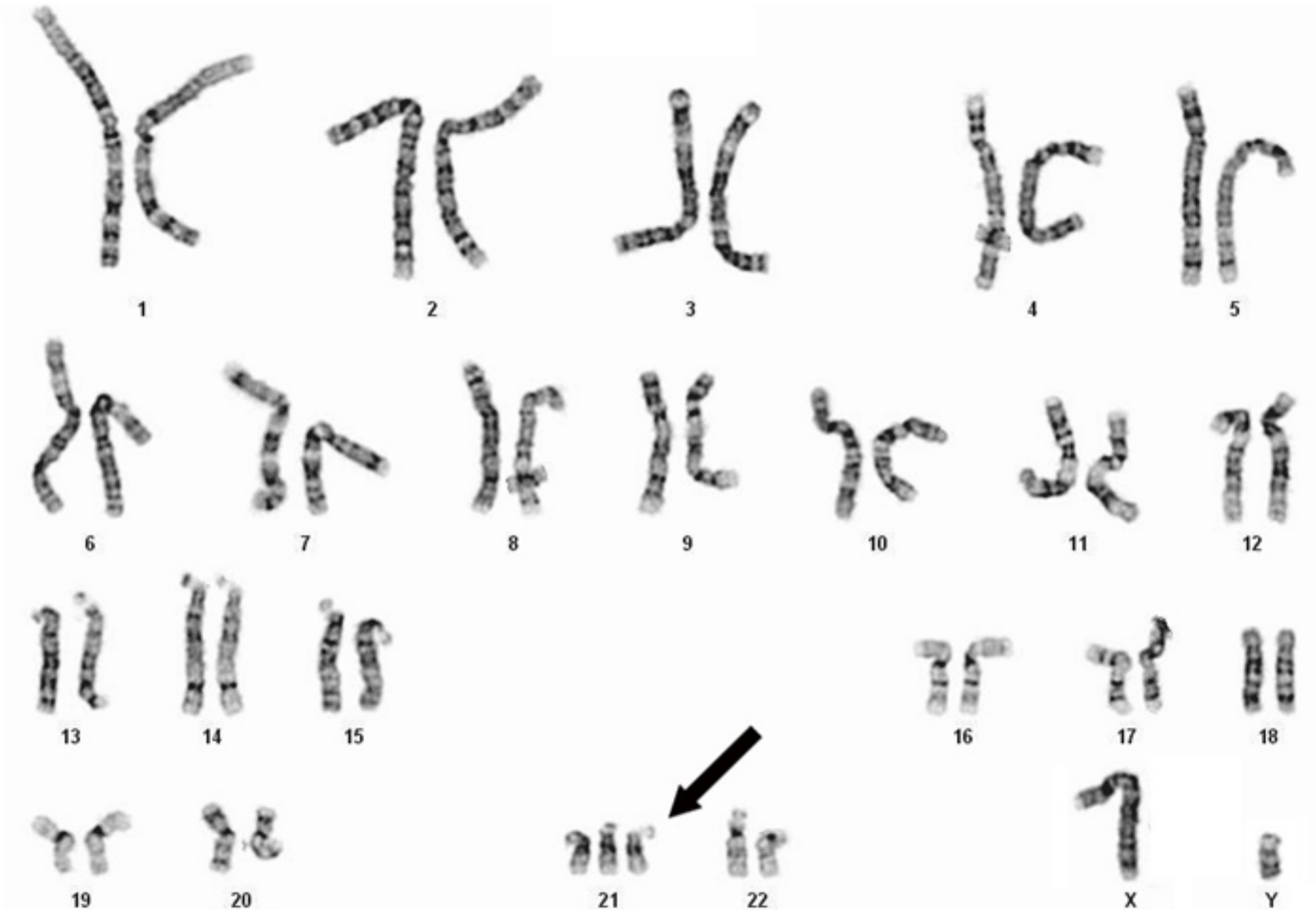

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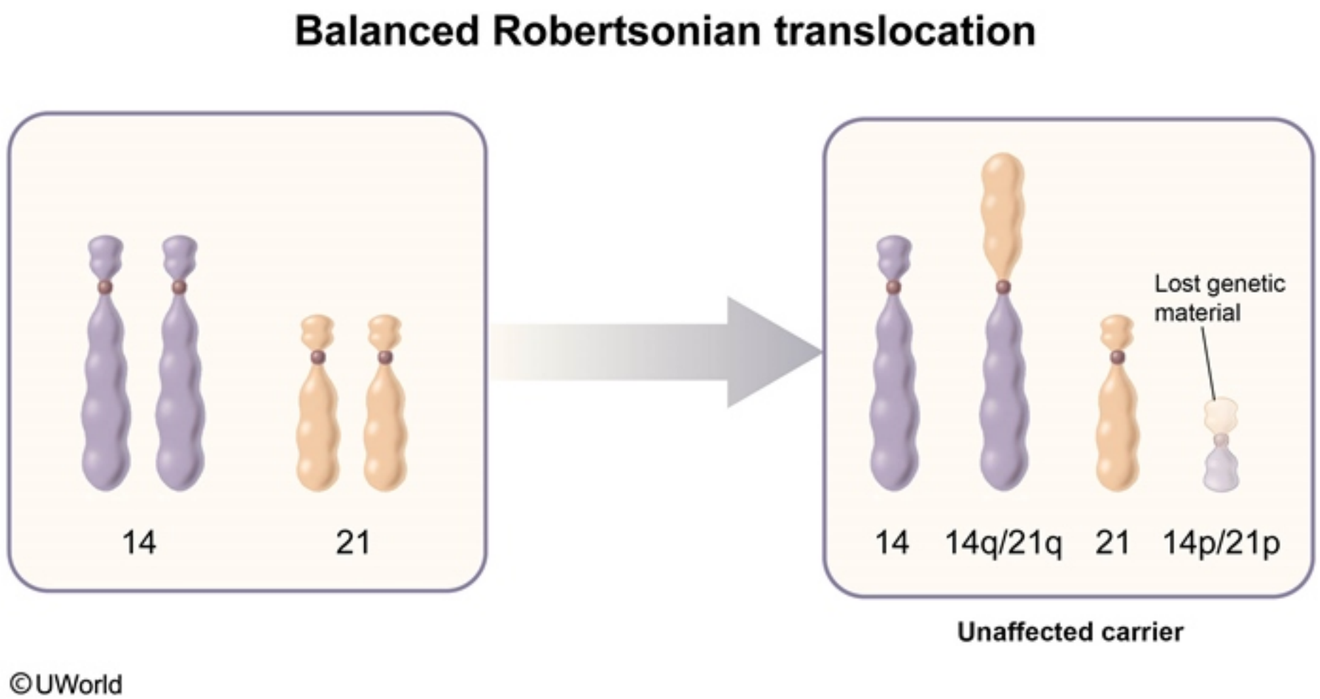

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Unbalanced Robertsonian translocations account for a minority of Down syndrome cases. Karyotyping shows 46 chromosomes with a

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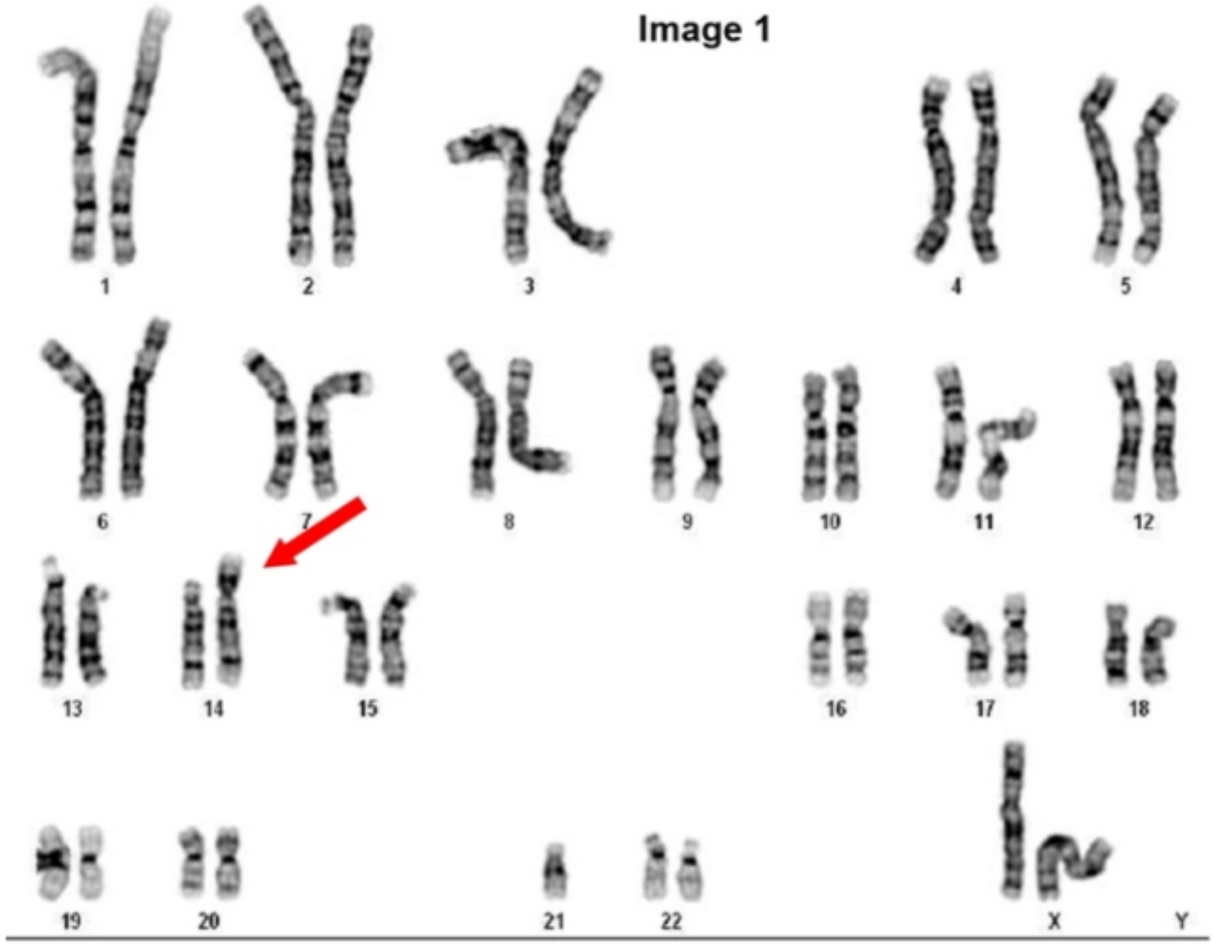

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Unbalanced Robertsonian translocations account for a minority of Down syndrome cases. Karyotyping shows 46 chromosomes with a

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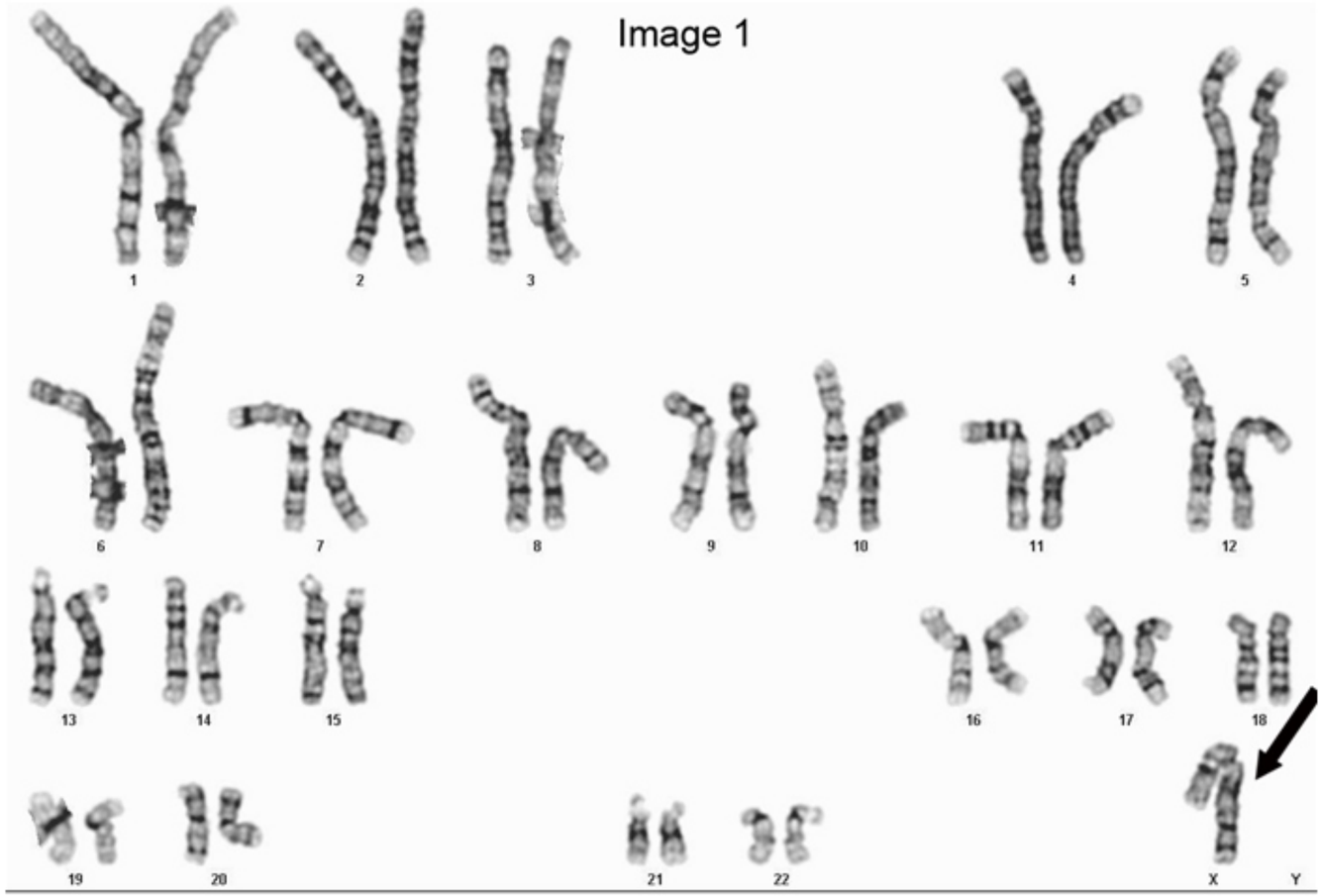

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Unbalanced Robertsonian translocations account for a minority of Down syndrome cases. Karyotyping shows 46 chromosomes with a

containing a normal set of chromosomes (ie, 1 copy of chromosome 21), the resultant fetus has an **unbalanced Robertsonian translocation** with **46 chromosomes** and **3 effective copies** of chromosome 21 [**46,XX, t(14;21)**]. Another possible maternal gamete includes 0 copies of

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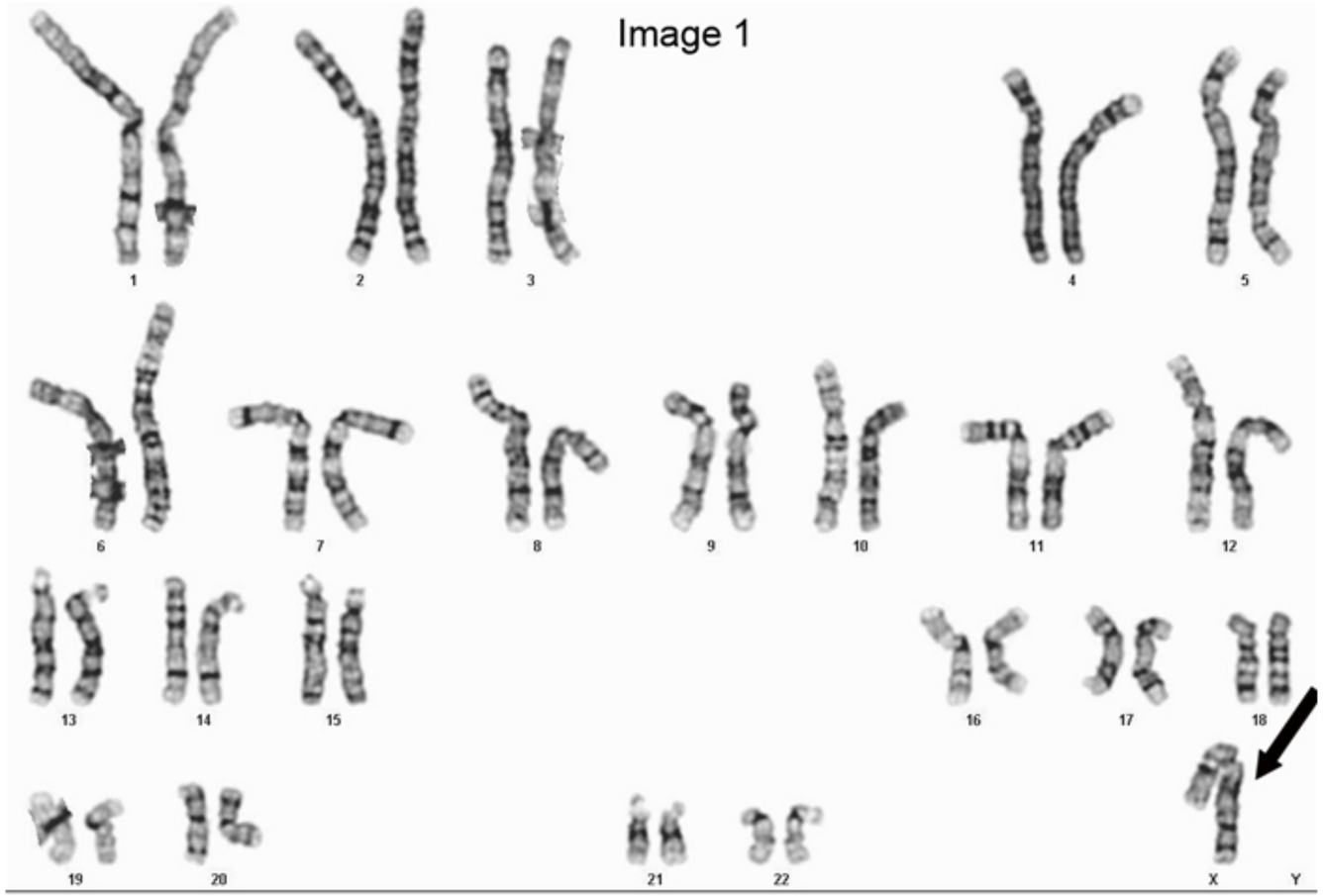

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A 16-year-old boy with mild intellectual disability is brought to the office to be evaluated for attention deficit-hyperactivity disorder. The parents state that he has always been impulsive and inattentive and that teachers are concerned about his inattentiveness and poor grades. Review of medical records shows a history of gross motor and speech delay for which he received physical and speech therapies during childhood. On physical examination, the boy has a long and narrow face, a prominent mandible, and large testes. There is hyperlaxity of his finger and thumb joints. Which of the following is the most likely diagnosis in this patient?

A. Down syndrome mosaicism
B. Ehlers-Danlos syndrome
C. Fragile X syndrome
D. Klinefelter syndrome
E. Marfan syndrome
F. Prader-Willi syndrome

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A. Down syndrome mosaicism (0%)
B. Ehlers-Danlos syndrome (9%)
✓ C. Fragile X syndrome (79%)
D. Klinefelter syndrome (3%)
E. Marfan syndrome (5%)
F. Prader-Willi syndrome (2%)

Omitted
Correct answer
C

79%
Answered correctly

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Explanation

Features of fragile X syndrome

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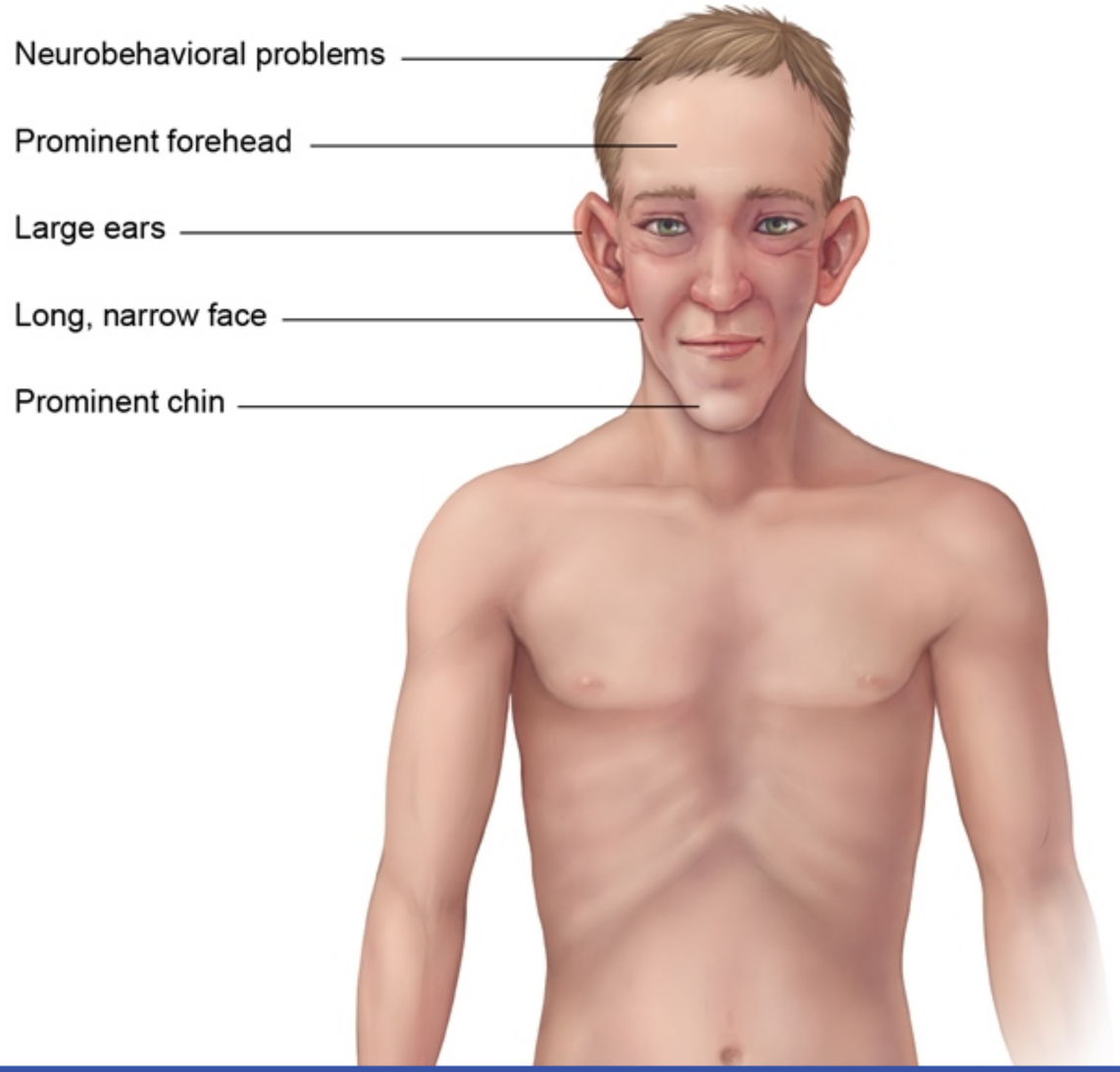
Features of fragile X syndrome



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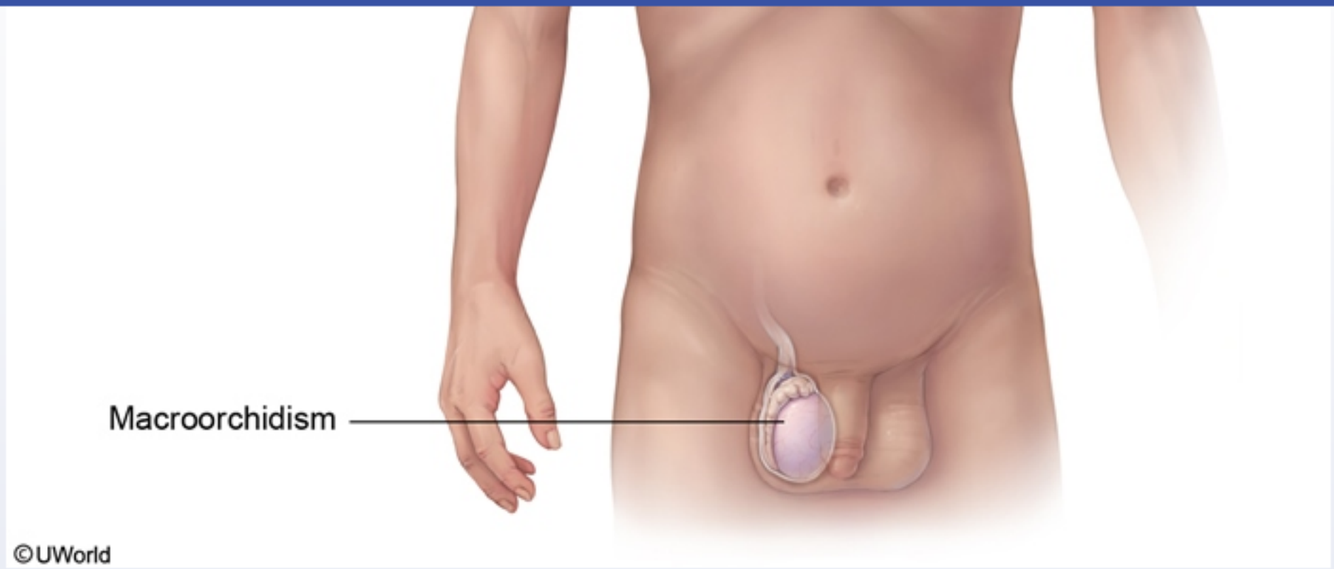

This patient has **fragile X syndrome** (FXS), the most common inherited and the second most common congenital cause of **intellectual disability**. FXS is an **X-linked** disorder caused by a loss-of-function mutation in the fragile X mental retardation 1 (*FMR1*) gene on the long arm of the X chromosome. Males who inherit the full mutation will manifest the features of FXS, whereas females with one abnormal X chromosome will have a milder and variable presentation.

The clinical features of FXS are most apparent after puberty in males; affected individuals have a **long, narrow face**, a **prominent forehead** and **chin**, and **large testes**. Patients often have **hyperlaxity** of the joints in the hand. **Developmental delay** (speech and motor) is common in infancy, but **neuropsychiatric features** often present in childhood (eg, anxiety, attention deficit-hyperactivity disorder, autism spectrum disorder).

(Choice A) Down syndrome, or trisomy 21, is the most common cause of congenital intellectual disability. In patients with Down syndrome mosaicism, some cells (but not all) have an extra copy of chromosome 21. These patients may have a milder presentation than those with classic Down syndrome.

(Choice B) Ehlers-Danlos syndrome is a connective tissue disorder that is most commonly due to defective type V collagen production. Patients typically have skin hyperelasticity and fragility as well as joint hyperlaxity. Ehlers-Danlos syndrome is not associated with intellectual disability.

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(Choice D) Patients with Klinefelter syndrome (47,XXY) often have mild intellectual disability in addition to tall stature, gynecomastia, small testes (often undescended), and infertility.

(Choice E) Marfan syndrome is an autosomal dominant connective tissue disorder characterized by tall stature, arachnodactyly (long and thin fingers), ectopia lentis (lens displacement), and dilation of the proximal aorta. Intellectual disability is not associated with Marfan syndrome.

(Choice F) Prader-Willi syndrome is an imprinting disorder caused by a paternal deletion of part of chromosome 15. In infancy, hypotonia and hyperphagia lead to gross motor delays and obesity, respectively. Intellectual disability and behavioral problems (eg, autistic-like behaviors, obsessive compulsive features) are common.

Educational objective:
Fragile X syndrome is an X-linked disorder that presents with a long, narrow face, a prominent chin and forehead, and large testes. Patients often have developmental delay and neuropsychiatric findings that overlap with anxiety disorders, autism, and attention deficit-hyperactivity disorder.

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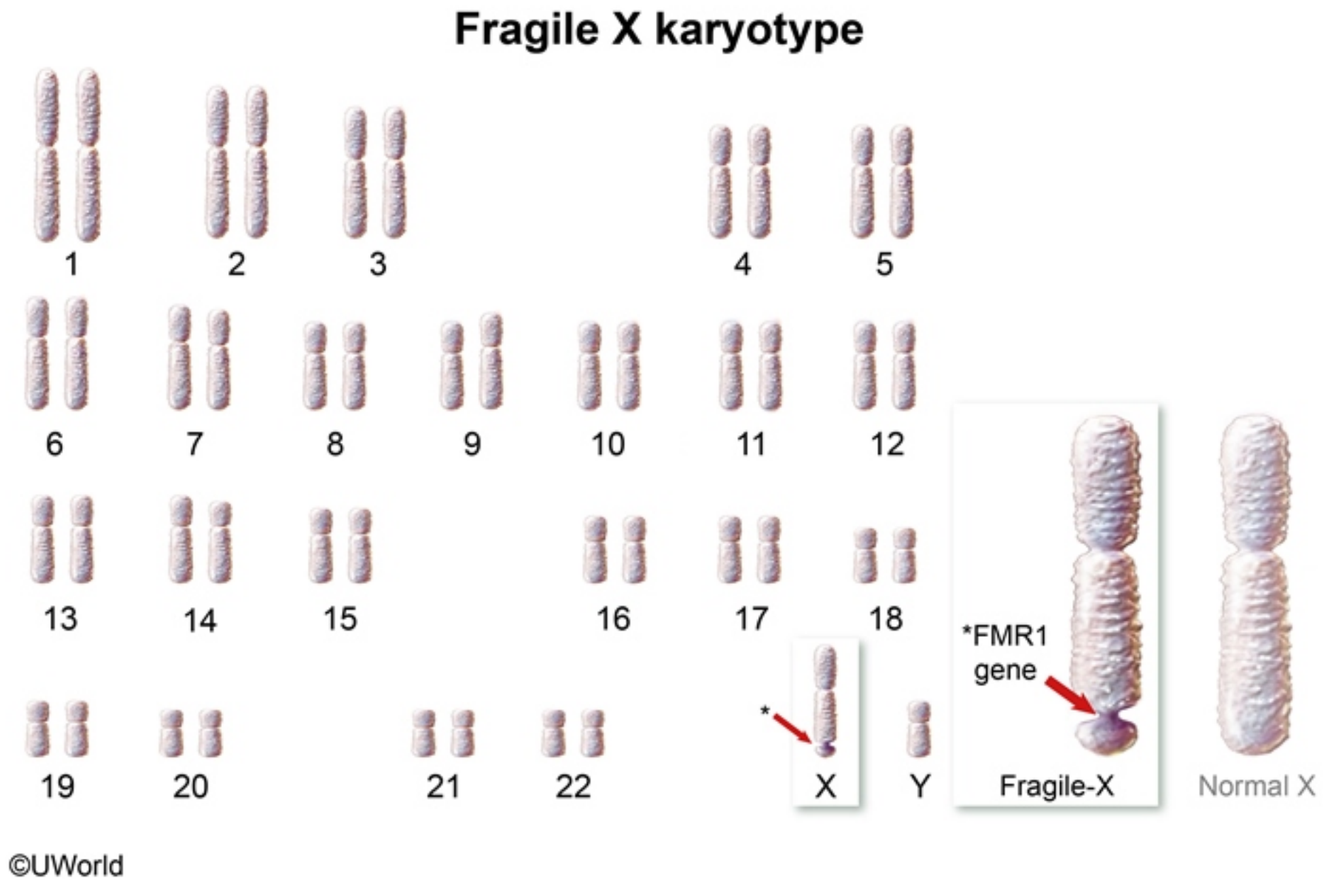

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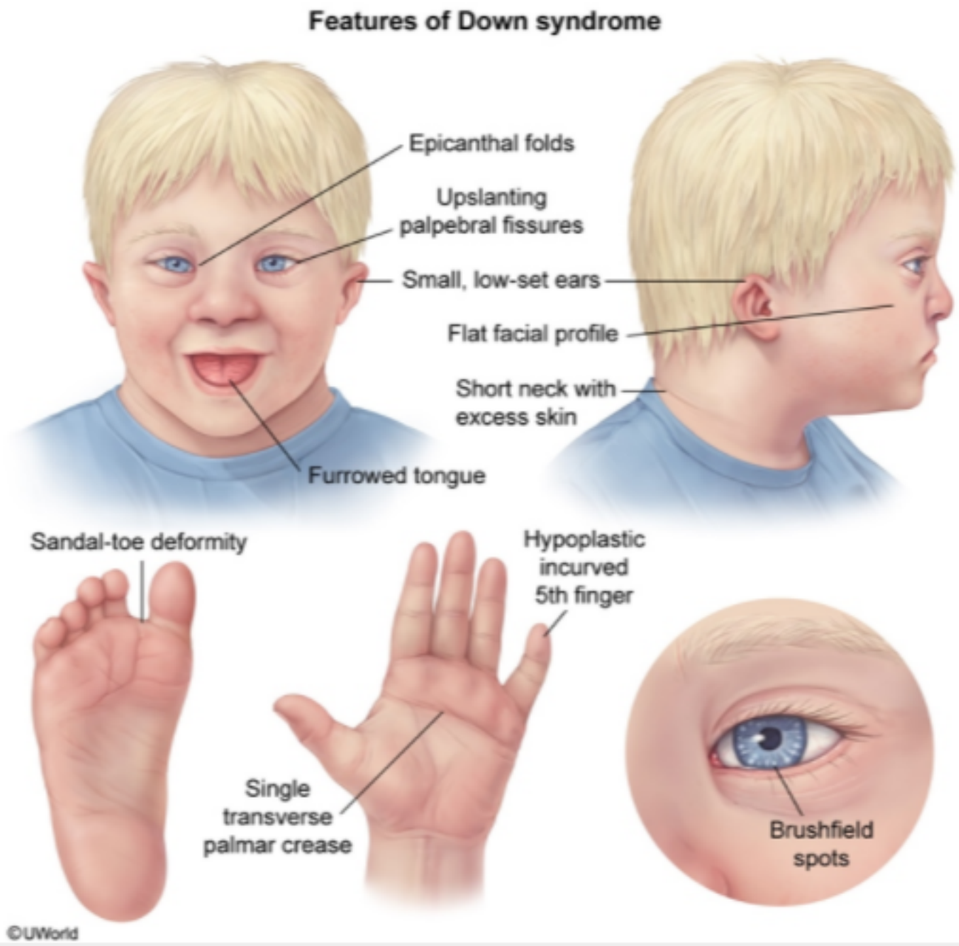

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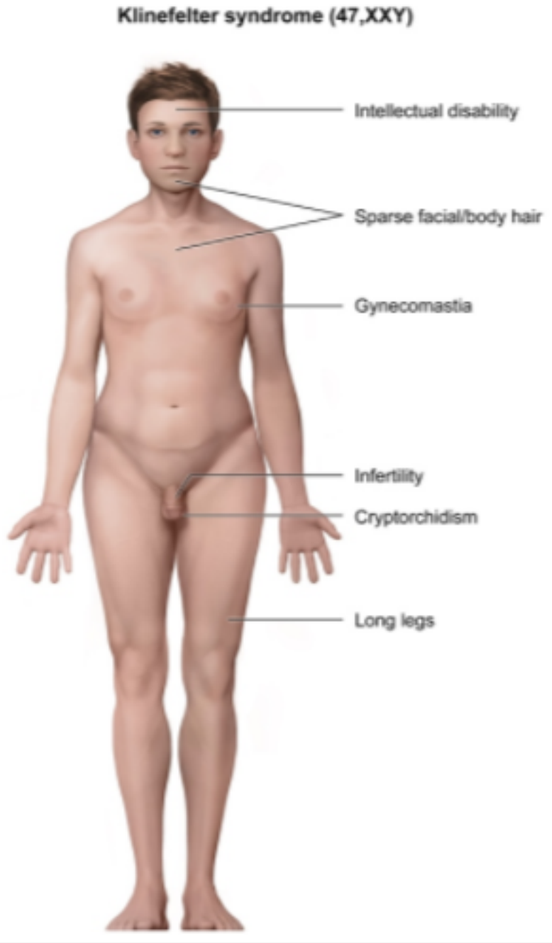

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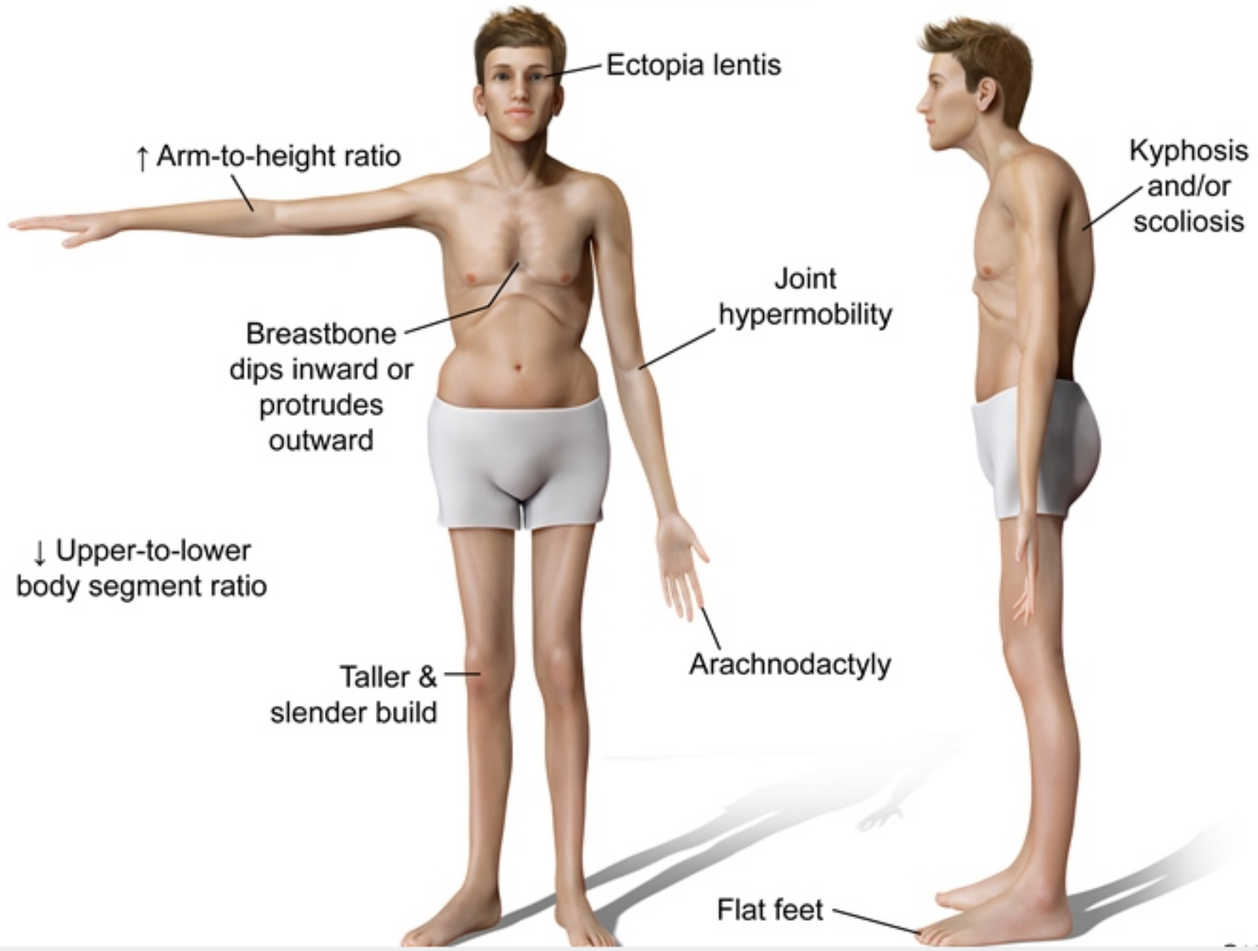

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Educational objective:
Fragile X syndrome is an X-linked disorder that presents with a long, narrow face, a prominent chin and forehead, and large testes. Patients often have developmental delay and neuropsychiatric findings that overlap with anxiety disorders, autism, and attention deficit-hyperactivity disorder.

References

- Fragile X syndrome.

Genetics	Nervous System	Fragile x syndrome
Subject	System	Topic

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A 41-year-old man with trisomy 21 is evaluated in the clinic due to cognitive decline. The patient has a history of moderate intellectual disability, but his higher cognitive functions have become progressively impaired in the past several years. He previously volunteered at a community library but recently lost his position as he could no longer perform his duties. The patient is now completely dependent on a caregiver for assistance with his activities of daily living such as getting dressed, bathing, and using the toilet. The patient keeps wandering in the group home and has become lost on several occasions. Which of the following is most likely to be increased in this patient?

A. Amyloid A protein

B. Amyloid precursor protein

C. Apolipoprotein E epsilon 4

D. CAG trinucleotide repeats

E. Islet amyloid polypeptide

Submit

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- A. Amyloid A protein (11%)
- ✓ B. Amyloid precursor protein (62%)
- C. Apolipoprotein E epsilon 4 (23%)
- D. CAG trinucleotide repeats (1%)
- E. Islet amyloid polypeptide (1%)

Omitted
Correct answer
B

62%
Answered correctly

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Last Updated

Explanation

Down syndrome comorbidities	
Neurology	• Intellectual disability • Early-onset Alzheimer disease

Explanation

Down syndrome comorbidities	
Neurology	• Intellectual disability • Early-onset Alzheimer disease
Cardiology	• Complete atrioventricular septal defect • Ventricular septal defect • Atrial septal defect
Gastroenterology	• Duodenal atresia • Hirschsprung disease
Endocrinology	• Hypothyroidism • Type 1 diabetes mellitus • Obesity
Hematology	• Acute leukemia
Rheumatology	• Atlantoaxial instability

Trisomy 21, also known as Down syndrome, is the most commonly diagnosed chromosomal anomaly in liveborn neonates. Typical symptoms include intellectual disability, congenital abnormalities (eg, gastrointestinal, cardiac), physical growth delay, and characteristic facial features (eg, flat facies, protruding tongue, epicanthic folds, oblique palpebral fissures). Many patients with trisomy 21 develop **early-onset Alzheimer disease (AD)**, defined as diagnosis of AD age ≤65, with some developing AD as early as the fourth decade of life.

Characteristic pathologic changes associated with AD involve accumulation of intracellular neurofibrillary tangles and extracellular amyloid-beta plaques:

- Neurofibrillary tangles are composed of tau protein, a primary component of intracellular microtubules. In AD, tau protein is

Rheumatology	• Atlantoaxial instability

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- Neurofibrillary tangles are composed of tau protein, a primary component of intracellular microtubules. In AD, tau protein is hyperphosphorylated, causing microtubule structures to collapse into "tangles" that contribute to global neuronal dysfunction.
- Amyloid beta is an abnormal fragment of **amyloid precursor protein**, which is normally involved in synaptic formation and repair. In AD, the protein is not properly cleared and forms amyloid fragments; these then harden into insoluble plaques that accumulate in brain tissue and vessel walls.

The amyloid precursor protein (*APP*) gene is located on **chromosome 21**. The **extra copy of *APP*** present in trisomy 21 is thought to accelerate amyloid accumulation and lead to early-onset AD.

(Choice A) Amyloid A protein is an acute-phase reactant that is associated with the development of multisystemic amyloidosis (AA amyloidosis) in reaction to chronic disease states (eg, rheumatoid arthritis, inflammatory bowel disease).

(Choice C) Apolipoprotein E is found in 3 allelic variations: epsilon 2, 3, and 4. Those with 1 or 2 copies of the epsilon 4 allele are at greater risk for late-onset AD (ie, AD diagnosed at age >65) compared with those without the allele.

(Choice D) Expansion of CAG trinucleotide repeats in the *HTT* gene, which codes for huntingtin protein, is responsible for Huntington disease. Individuals with this condition typically have movement abnormalities (eg, chorea), psychiatric symptoms, and dementia.

(Choice E) Islet amyloid polypeptide is a normal secretory product of pancreatic beta cells that forms cytotoxic deposits in type 2 diabetes mellitus, impairing beta-cell function.

Educational objective:

Characteristic pathologic changes associated with AD involve accumulation of intracellular neurofibrillary tangles and extracellular amyloid-beta plaques:

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Educational objective:
Patients with trisomy 21 (Down syndrome) have 3 copies of the amyloid precursor protein gene located on chromosome 21. This increases amyloid-beta accumulation in the brain, placing these patients at high risk for developing early-onset Alzheimer disease.

References

- Aging in Down syndrome and the development of Alzheimer's disease neuropathology.

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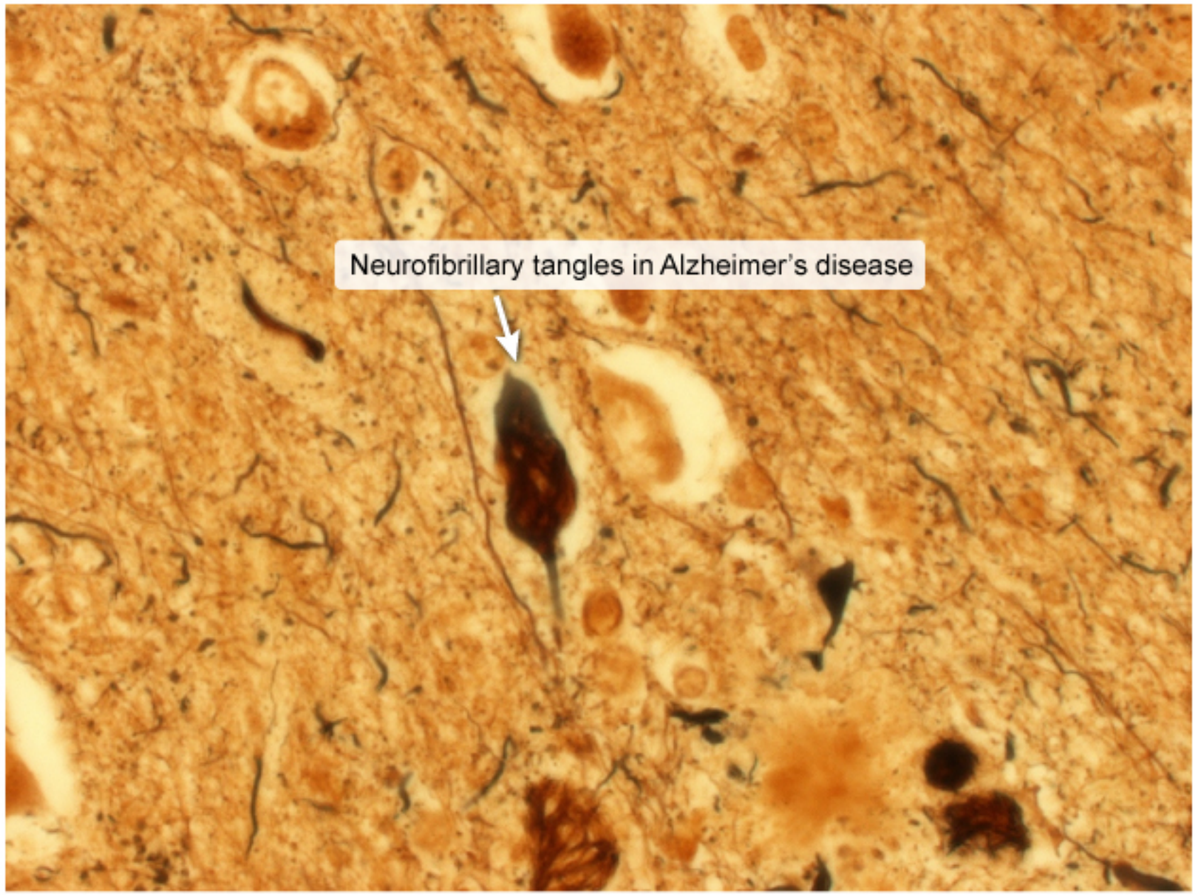
Alzheimer's disease



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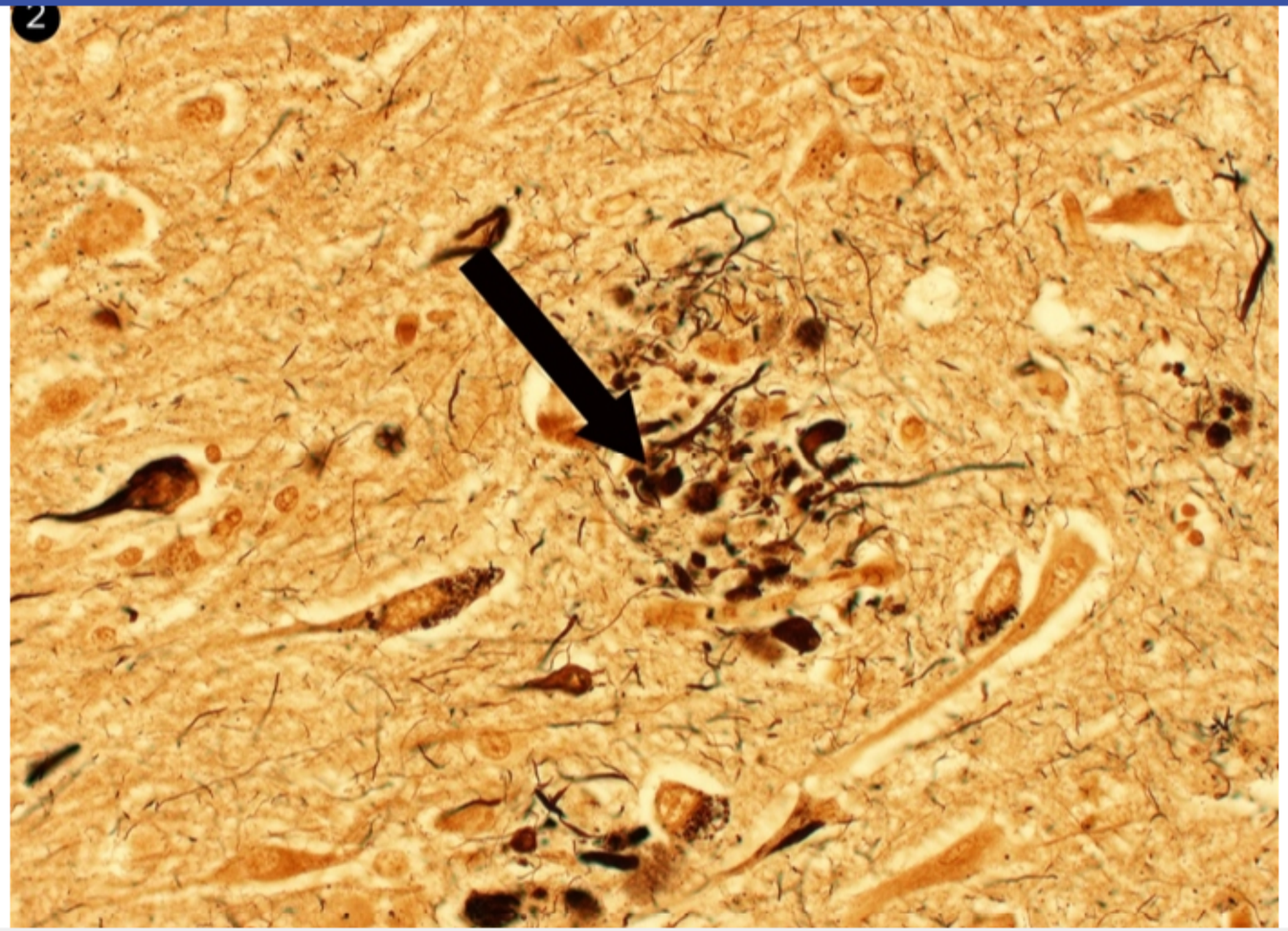

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hyperphosphorylated, causing microtubule structures to collapse into "tangles" that contribute to global neuronal dysfunction.

- Amyloid beta is an abnormal fragment of **amyloid precursor protein**, which is normally involved in synaptic formation and repair. In AD, the protein is not properly cleared and forms amyloid fragments; these then harden into insoluble plaques that accumulate in brain tissue and vessel walls.

The amyloid precursor protein (*APP*) gene is located on **chromosome 21**. The **extra copy of *APP*** present in trisomy 21 is thought to accelerate amyloid accumulation and lead to early-onset AD.

(Choice A) Amyloid A protein is an acute-phase reactant that is associated with the development of multisystemic amyloidosis (AA amyloidosis) in reaction to chronic disease states (eg, rheumatoid arthritis, inflammatory bowel disease).

(Choice C) Apolipoprotein E is found in 3 allelic variations: epsilon 2, 3, and 4. Those with 1 or 2 copies of the epsilon 4 allele are at greater risk for late-onset AD (ie, AD diagnosed at age >65) compared with those without the allele.

(Choice D) Expansion of CAG trinucleotide repeats in the *HTT* gene, which codes for huntingtin protein, is responsible for Huntington disease. Individuals with this condition typically have movement abnormalities (eg, chorea), psychiatric symptoms, and dementia.

(Choice E) Islet amyloid polypeptide is a normal secretory product of pancreatic beta cells that forms cytotoxic deposits in type 2 diabetes mellitus, impairing beta-cell function.

Educational objective:
Patients with trisomy 21 (Down syndrome) have 3 copies of the amyloid precursor protein gene located on chromosome 21. This increases amyloid-beta accumulation in the brain, placing these patients at high risk for developing early-onset Alzheimer disease.

References

- Aging in Down syndrome and the development of Alzheimer's disease neuropathology.

Genetics	Nervous System	Down syndrome
Subject	System	Topic

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A 60-year-old man comes to the office due to dark, rusty-colored urine for the last 2 weeks. He reports no pain, urinary frequency, or urgency. The patient has no chronic medical conditions and takes no medications. He smoked a half pack of cigarettes daily for 10 years but quit 30 years ago. His father had hypertension and his mother has Alzheimer dementia. Urinalysis shows a large number of red blood cells. Renal ultrasound reveals a mass in the right kidney. Cytologic evaluation of the mass shows malignant cells with a chromosome 3p deletion. The deletion most likely involves which of the following genes?

A. *c-MYC*

B. *NF-1*

C. *RB*

D. *VHL*

E. *WT-1*

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A. *c-MYC* (7%)
B. *NF-1* (2%)
C. *RB* (5%)
✓ D. *VHL* (76%)
E. *WT-1* (7%)

Omitted
Correct answer
D

76%
Answered correctly

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02/21/2020
Last Updated

Explanation

Common hereditary cancer syndromes			
Syndrome	**Gene**	**Associated neoplasms**	**Pathogenesis**

Common hereditary cancer syndromes

Syndrome	Gene	Associated neoplasms	Pathogenesis
Lynch syndrome	*MSH2, MLH1, MSH6, PMS2*	• Colorectal cancer • Endometrial cancer • Ovarian cancer	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Familial adenomatous polyposis	*APC*	• Colorectal cancer • Desmoids & osteomas • Brain tumors	
von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic	

von Hippel-Lindau syndrome	*VHL*	• Hemangioblastomas • Clear cell renal carcinoma • Pheochromocytoma	• **Autosomal dominant** • Caused by **inactivating** mutation in corresponding **tumor suppressor gene** • Deletion of remaining normal allele (**second hit**) leads to loss of heterozygosity & **malignant transformation**
Li-Fraumeni syndrome	*TP53*	• Sarcomas • Breast cancer • Brain tumors • Adrenocortical carcinoma • Leukemia	
Multiple endocrine neoplasia type 1	*MEN1*	• Parathyroid adenomas • Pituitary adenomas • Pancreatic adenomas	
Multiple endocrine neoplasia type 2	*RET*	• Medullary thyroid cancer • Pheochromocytoma • Parathyroid hyperplasia (*MEN2A*)	• **Autosomal dominant** • **Activating** (gain-of-function) mutation in proto-oncogene • **Continuous stimulation** of cell division predisposes to tumor growth

This patient with hematuria and a malignant renal mass most likely has **renal cell carcinoma** (RCC). RCC, particularly the **clear cell subtype**, is strongly associated with deletion, nonsense, and frameshift mutations involving the **von Hippel-Lindau (*VHL*)** gene at chromosome 3p. The majority of RCCs are sporadic and develop as single tumors; these are typically associated with somatic mutations in the *VHL* gene. Germline *VHL* mutations also occur and are responsible for von Hippel-Lindau syndrome, a rare, autosomal dominant disorder characterized by clear cell

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VHL encodes a protein that normally inhibits hypoxia-inducible factors; *VHL* mutations lead to constitutive activation of these proteins, resulting in overexpression of multiple **angiogenic growth factors** (eg, VEG-F, PDG-F) that stimulate tumor proliferation. As a result, tumors harboring VHL mutations are highly sensitive to **angiogenesis inhibitors**.

(Choice A) *c-MYC* is an oncogene located on chromosome 8. Mutations are associated with Burkitt lymphoma and diffuse large B-cell lymphoma.

(Choice B) *NF-1* is a tumor suppressor gene located on chromosome 17. Mutations of this gene cause neurofibromatosis type 1.

(Choice C) The *RB* tumor suppressor gene (antioncogene) is located on chromosome 13. Mutations of this gene lead to the development of retinoblastoma and osteosarcoma.

(Choice E) Mutations of the *WT-1* tumor suppressor gene are associated with the development of Wilms tumor. This gene is located on chromosome 11.

Educational objective:
Sporadic and hereditary (associated with von Hippel-Lindau disease) renal cell carcinomas are associated with mutations involving the *VHL* gene on chromosome 3p. The *VHL* gene is a tumor suppressor that inhibits hypoxia-inducible factors; mutations lead to constitutive activation of these proteins, resulting in the activation of multiple angiogenic and tumorigenic growth factors (eg, VEG-F, PDG-F).

References

- VHL and hypoxia signaling: beyond HIF in cancer.

Genetics Renal, Urinary Systems & Electrolytes Renal cell carcinoma

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A 23-year-old previously healthy man comes to the office after noticing a painless, hard mass in the left testis. Scrotal ultrasound shows a solid testicular mass, and CT scan of the abdomen and pelvis shows left paraaortic lymphadenopathy. Left orchidectomy is performed and postoperative histopathology reveals seminoma of the testis. External beam radiotherapy is administered to the paraaortic metastatic area. Several weeks later, the retroperitoneal nodes are observed to have markedly decreased in size. Which of the following is the most likely effect of the therapy used on the metastatic cells in this patient?

A. Demethylation of DNA
B. DNA cross-linking
C. Double-strand DNA breaks
D. Nucleotide mismatches
E. Pyrimidine dimers

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- A. Demethylation of DNA (4%)
- B. DNA cross-linking (10%)
- ✓ C. Double-strand DNA breaks (64%)
- D. Nucleotide mismatches (2%)
- E. Pyrimidine dimers (17%)

Omitted
Correct answer
C

64%
Answered correctly

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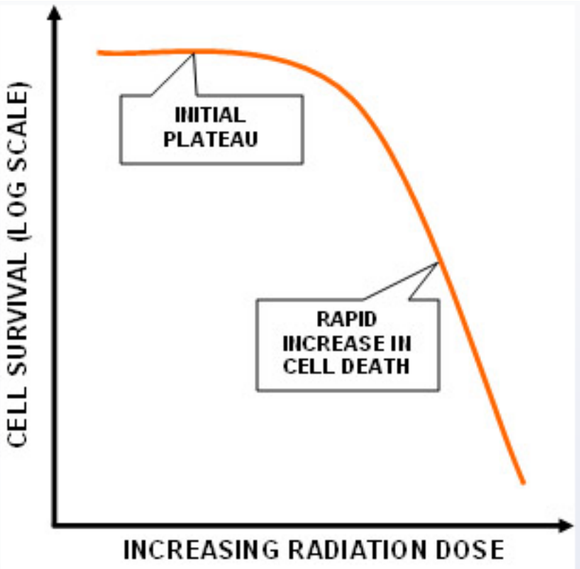
Time Spent

06/13/2020
Last Updated

Explanation



Therapeutic **ionizing radiation** (eg, gamma rays, x-rays), commonly used to treat or palliate several types of cancer, can cause cell death through 2 major mechanisms:

- DNA **double-strand breakage**: Breakage of both strands is generally required, as single strand breaks are readily repaired by polymerases.
- Free radical formation: Reactive oxygen species are formed by ionization of water; oxygen free radicals are then able to cause cellular and DNA damage.

The effect of radiation is most pronounced in malignant cells as they are rapidly dividing and consequently less able to repair DNA damage. Epithelial surfaces (eg, bowel mucosa, skin) are also severely affected because they are rapidly dividing.

A characteristic cell death curve of exposure to radiation shows a nearly flat line on initial exposure, followed by a steep increase in cell death as the radiation dose increases (Diagram). The steep portion is due to a sharp increase in double-stranded DNA strand fractures and oxygen free radicals.

(Choice A) DNA methylation (only cytosine and adenine) typically inhibits gene transcription. Demethylation or hypomethylation of oncogenes

INCREASING RADIATION DOSE

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(Choice A) DNA methylation (only cytosine and adenine) typically inhibits gene transcription. Demethylation or hypomethylation of oncogenes (and hypermethylation of tumor suppressor genes) contributes to the development of some cancers.

(Choice B) DNA cross-linking can be induced by numerous chemical and physical agents, notably alkylating agents used in cancer treatment.

(Choice D) During DNA replication, incorrect base placement can occur, but enzymes scan the newly synthesized DNA strands for mismatched bases, which are then excised and replaced. This process is guided by the presence of adenine methylation (recognized by the enzymes) in the template strand, as the daughter strand remains unmethylated for some time following DNA replication.

(Choice E) DNA damage from exposure to ultraviolet radiation, a non-ionizing radiation, leads to the formation of pyrimidine-pyrimidine dimers (thymine dimers). Ionizing radiation has higher energy (enough to remove an electron), leading to more cell damage.

Educational objective:
Exposure to ionizing radiation, including therapeutic and palliative radiation therapy, induces DNA damage through DNA double-strand fractures and the formation of oxygen free radicals.

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Educational objective:
Exposure to ionizing radiation, including therapeutic and palliative radiation therapy, induces DNA damage through DNA double-strand fractures and the formation of oxygen free radicals.

Genetics	Hematology & Oncology	Radiation injury
Subject	System	Topic

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A 24-year-old African American woman comes to the office with her husband for prenatal counseling. She has a 3-year-old child with sickle cell anemia from a previous marriage, and the child's father died in a car accident. The patient remarried last year and is interested in having more children. She and her new husband do not have sickle cell anemia, and the patient's husband has no other children. However, the patient and her husband are worried that their future children could have sickle cell anemia. A urine pregnancy test is negative. Which of the following is the best initial test that can be offered to this couple?

A. Chorionic villous sampling during future pregnancy
B. Maternal hemoglobin electrophoresis
C. Northern blot analysis of paternal blood sample
D. Paternal hemoglobin electrophoresis
E. Paternal karyotype analysis

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A. Chorionic villous sampling during future pregnancy (2%)

B. Maternal hemoglobin electrophoresis (19%)

C. Northern blot analysis of paternal blood sample (5%)

✓ D. Paternal hemoglobin electrophoresis (68%)

E. Paternal karyotype analysis (3%)

Omitted
Correct answer
D

68%
Answered correctly

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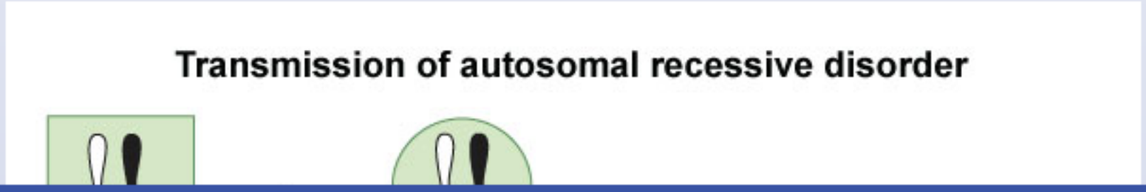
01/14/2020
Last Updated

Explanation



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Transmission of autosomal recessive disorder

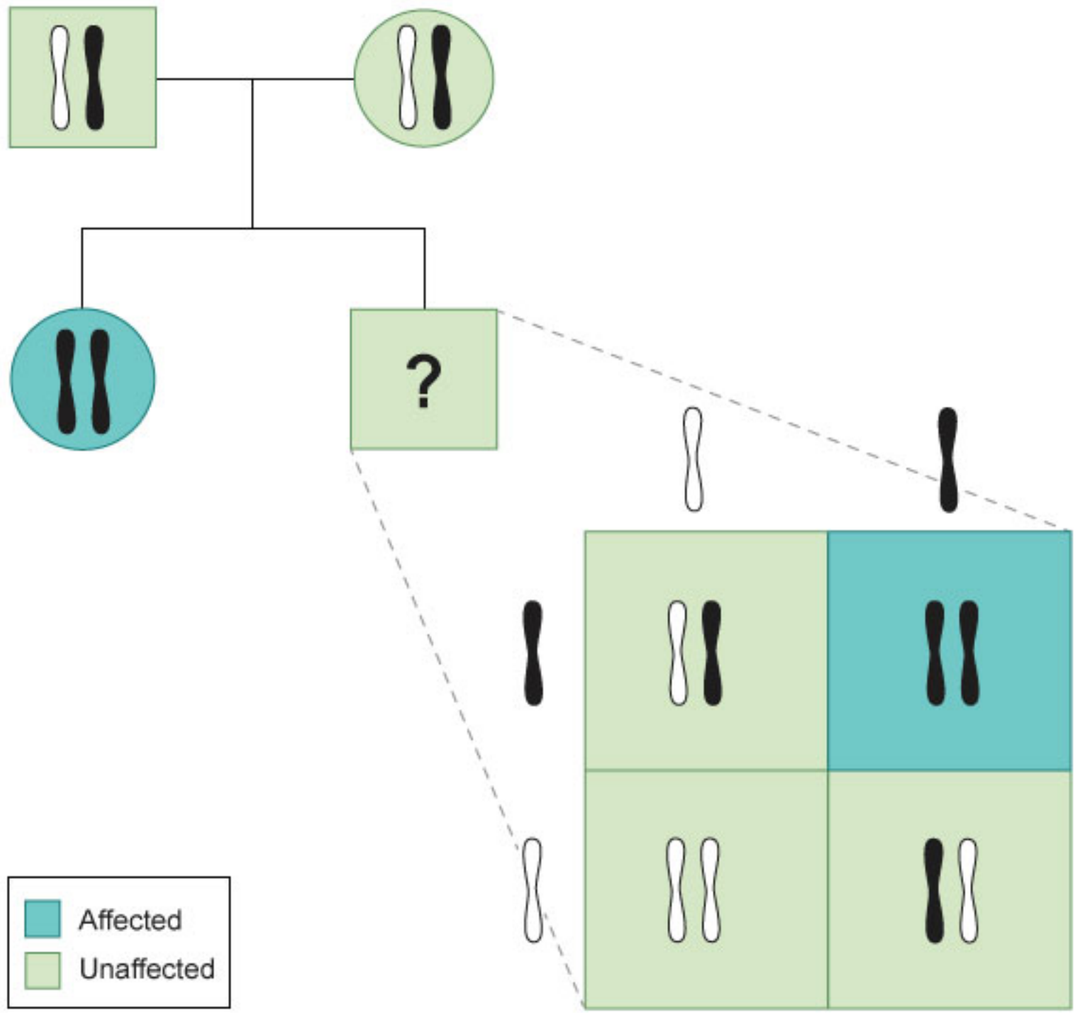

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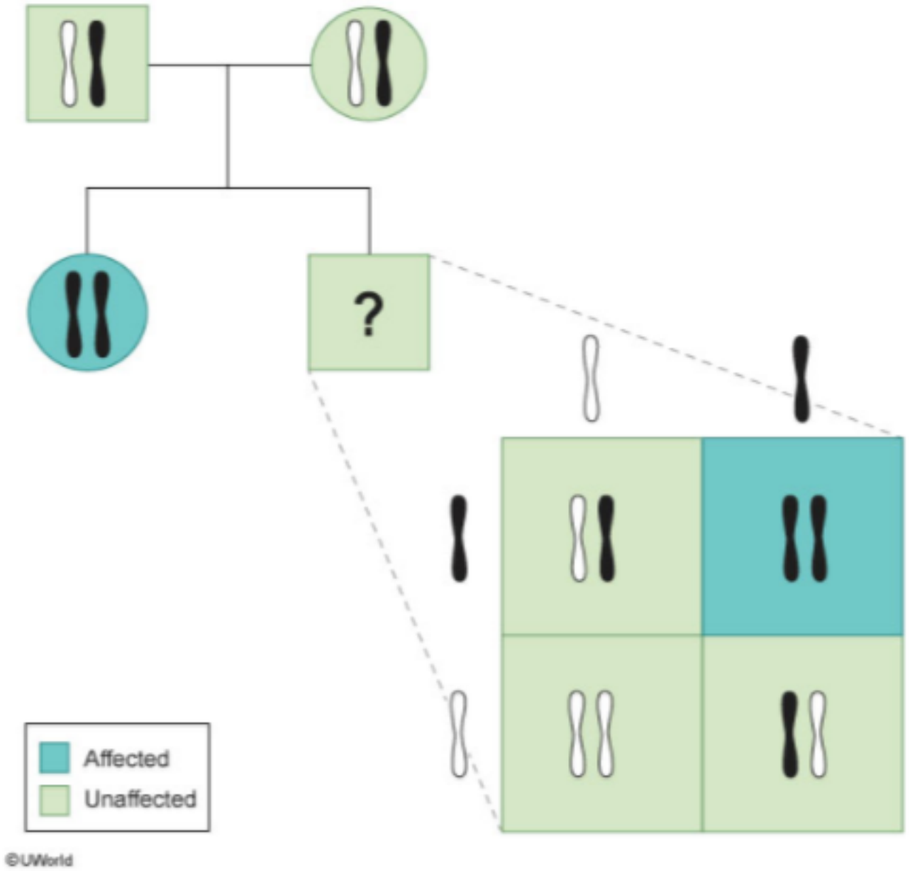
Exhibit Display

Transmission of autosomal recessive disorder



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Sickle cell anemia is an **autosomal recessive** hemoglobinopathy. Affected patients must inherit 2 mutant genes for hemoglobin S (HbS), one from each parent. In order for an offspring of 2 parents without sickle cell anemia to be affected, **both parents must carry the sickle cell trait**. Any offspring resulting from such pairings will have a 1 in 4 chance of having sickle cell disease (SCD). This patient is a carrier of the sickle cell trait as she has a child with sickle cell anemia.

Hemoglobin electrophoresis, a type of gel electrophoresis, is used to determine if the patient's new husband also has sickle cell trait. Abnormal hemoglobin (eg, HbS), moves at a slower speed than normal hemoglobin due to the replacement of glutamic acid by valine. The husband's test results combined with the maternal family history will determine the risk that future offspring will inherit sickle cell anemia.

(Choice A) The chorionic villi are part of the placenta and, as such, are fetal tissue. Once fetal DNA is obtained, DNA sequencing can be performed to evaluate for sickle cell mutation. Chorionic villus sampling (CVS) can be performed at 10-14 weeks gestation. However, it is relatively invasive and carries a risk of miscarriage, spotting/bleeding, infection, and other complications. CVS is not helpful to a patient who wishes to determine her risk prior to conception.

(Choice B) It is not necessary to perform maternal hemoglobin electrophoresis as it has been established from this patient's history that she has sickle cell trait.

(Choice C) Northern blots use electrophoresis to separate RNA by size, followed by the application of a DNA probe to detect a specific RNA molecule. This allows for the quantification of the RNA expression of specific genes. Hemoglobin electrophoresis is a more appropriate test for SCD as it involves the separation of protein (eg, hemoglobin) rather than RNA.

(Choice E) A karyotype is a visual analysis of all the chromosomes in a cell ordered by size and stained to reveal chromosomal banding. SCD results from a single nucleotide mutation, not from any abnormality in overall chromosome structure. Disorders due to chromosomal abnormalities include Klinefelter syndrome (47,XXY), Turner syndrome (45,XO) and trisomy disorders.

Educational objective:
Sickle cell anemia is an autosomal recessive hemoglobinopathy. In order for a child to have sickle cell disease, both parents must be carriers. Hemoglobin electrophoresis can be used to determine the carrier status of a prospective parent who has no history of sickle cell anemia.

References

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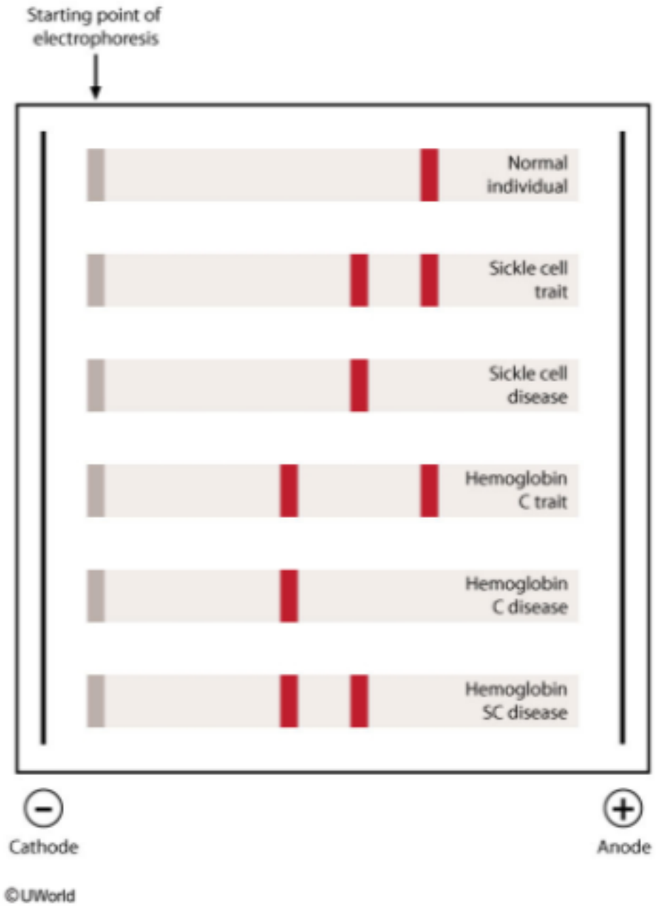
Hemoglobinopathy electrophoresis patterns



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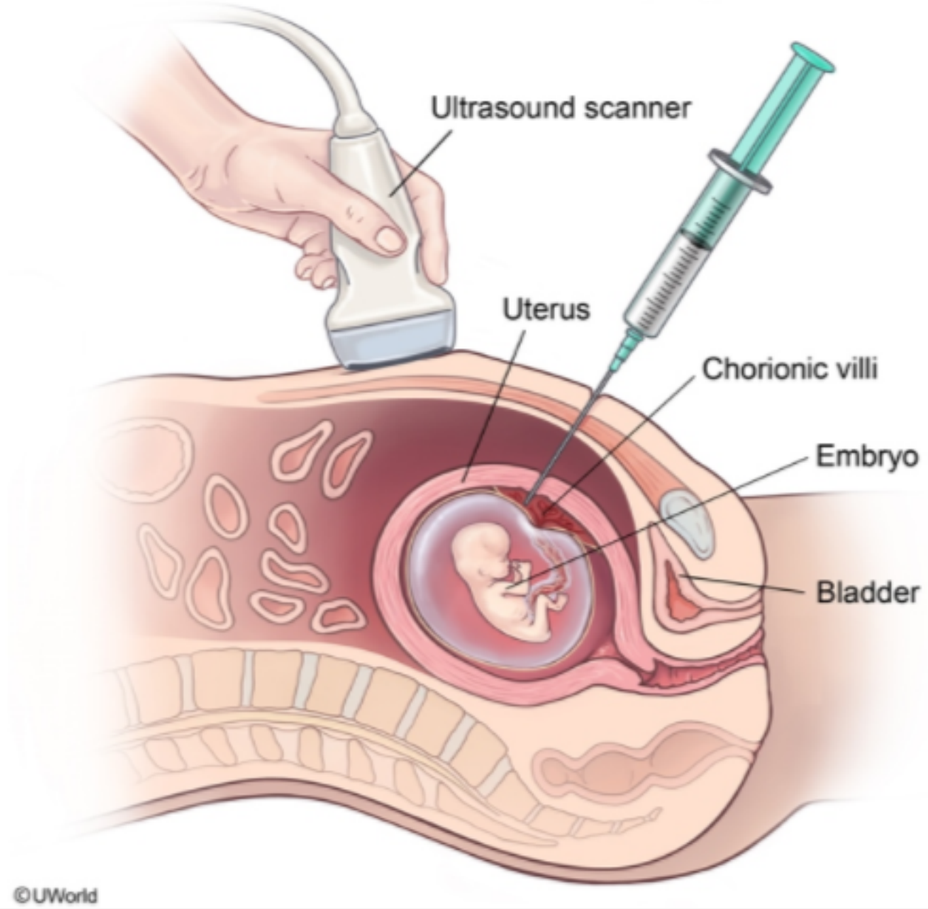
Chorionic villus sampling



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References

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Sickle cell anemia is an autosomal recessive hemoglobinopathy. In order for a child to have sickle cell disease, both parents must be carriers. Hemoglobin electrophoresis can be used to determine the carrier status of a prospective parent who has no history of sickle cell anemia.

References

- Diagnosis of the haemoglobinopathies.
- Diagnostic approach to hemoglobinopathies.

Genetics	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 23-year-old asymptomatic male participates in clinical research and is found to be homozygous for the apolipoprotein E-4 allele. In the future, this patient is most likely to suffer from which of the following?

- A. Familial hypercholesterolemia
- B. Hypertrophic cardiomyopathy
- C. Diabetes mellitus, type 2
- D. Peptic ulcer disease
- E. Polycystic kidney disease
- F. Alzheimer dementia

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A 23-year-old asymptomatic male participates in clinical research and is found to be homozygous for the apolipoprotein E-4 allele. In the future, this patient is most likely to suffer from which of the following?

- A. Familial hypercholesterolemia (31%)
- B. Hypertrophic cardiomyopathy (1%)
- C. Diabetes mellitus, type 2 (3%)
- D. Peptic ulcer disease (0%)
- E. Polycystic kidney disease (1%)
- ✓ F. Alzheimer dementia (62%)

Omitted
Correct answer
F

62%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Alzheimer disease has a strong genetic predisposition. About 30% of patients have a family history of the disease. According to age when symptoms begin, Alzheimer disease can be classified as early or late. The following three mutation sites have been associated with early-onset familial Alzheimer disease (onset <60 years old):

1. Amyloid precursor protein (APP) gene on chromosome 21
2. Presenilin 1 gene on chromosome 14

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2. Presenilin 1 gene on chromosome 14
3. Presenilin 2 gene on chromosome 1

Both APP and presenilin gene mutations are thought to promote the production of A β-amyloid.

Late-onset familial Alzheimer disease is associated with the ε4 allele of Apolipoprotein E. The exact mechanism of its influence is not known. It is thought that the ApoE4 protein may be involved in the formation of senile plaques.

(Choice A) Familial hypercholesterolemia is an autosomal dominant disorder. It is associated with a defect in low-density lipoprotein (LDL) receptors. This defect leads to decreased hepatic LDL uptake and severe elevation in total cholesterol and LDL levels.

(Choice B) Hypertrophic cardiomyopathy is a familial disorder inherited as an autosomal dominant trait. The most common mutation is of the β-myosin heavy chain.

(Choice C) Genetic factors play an important role in diabetes mellitus type 2 (more important than in type 1). Genetic predisposition to increased insulin resistance and deranged insulin secretion by β-cells are important precursors to disease.

(Choice D) Peptic ulcer disease is strongly associated with *H. pylori* infection, but not ApoE4.

(Choice E) Polycystic kidney disease can be inherited as autosomal recessive (also called infantile form) or dominant trait (adult form). Neither of these conditions is associated with ApoE4.

Educational Objective:
Early-onset familial Alzheimer disease is associated with three gene mutations: APP (chromosome 21), presenilin 1 and presenilin 2. Late-onset familial Alzheimer disease is associated with apolipoprotein E4 genotype.

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2. Presenilin 1 gene on chromosome 14
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(Choice E) Polycystic kidney disease can be inherited as autosomal recessive (also called infantile form) or dominant trait (adult form). Neither of these conditions is associated with ApoE4.

Educational Objective:
Early-onset familial Alzheimer disease is associated with three gene mutations: APP (chromosome 21), presenilin 1 and presenilin 2. Late-onset familial Alzheimer disease is associated with apolipoprotein E4 genotype.

Genetics	Nervous System	Alzheimer disease
Subject	System	Topic

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A 33-year old primigravida comes to the office to discuss results of prenatal testing. The patient is at 12 weeks gestation based on her last menstrual period. She has been taking prenatal vitamins inconsistently due to pregnancy-related nausea. Maternal alpha-fetoprotein level is reduced, and an ultrasound reveals increased nuchal translucency. Chorionic villous sampling shows a fetal karyotype of 47, XX, +21. The fetus is at greatest risk of developing which of the following conditions?

A. Duodenal atresia
B. Holoprosencephaly
C. Myelomeningocele
D. Nephroblastoma
E. Omphalocele
F. Pyloric stenosis

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- ✓ A. Duodenal atresia (83%)
- B. Holoprosencephaly (2%)
- C. Myelomeningocele (4%)
- D. Nephroblastoma (1%)
- E. Omphalocele (3%)
- F. Pyloric stenosis (4%)

Omitted
Correct answer
A

83%
Answered correctly

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Time Spent

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Explanation

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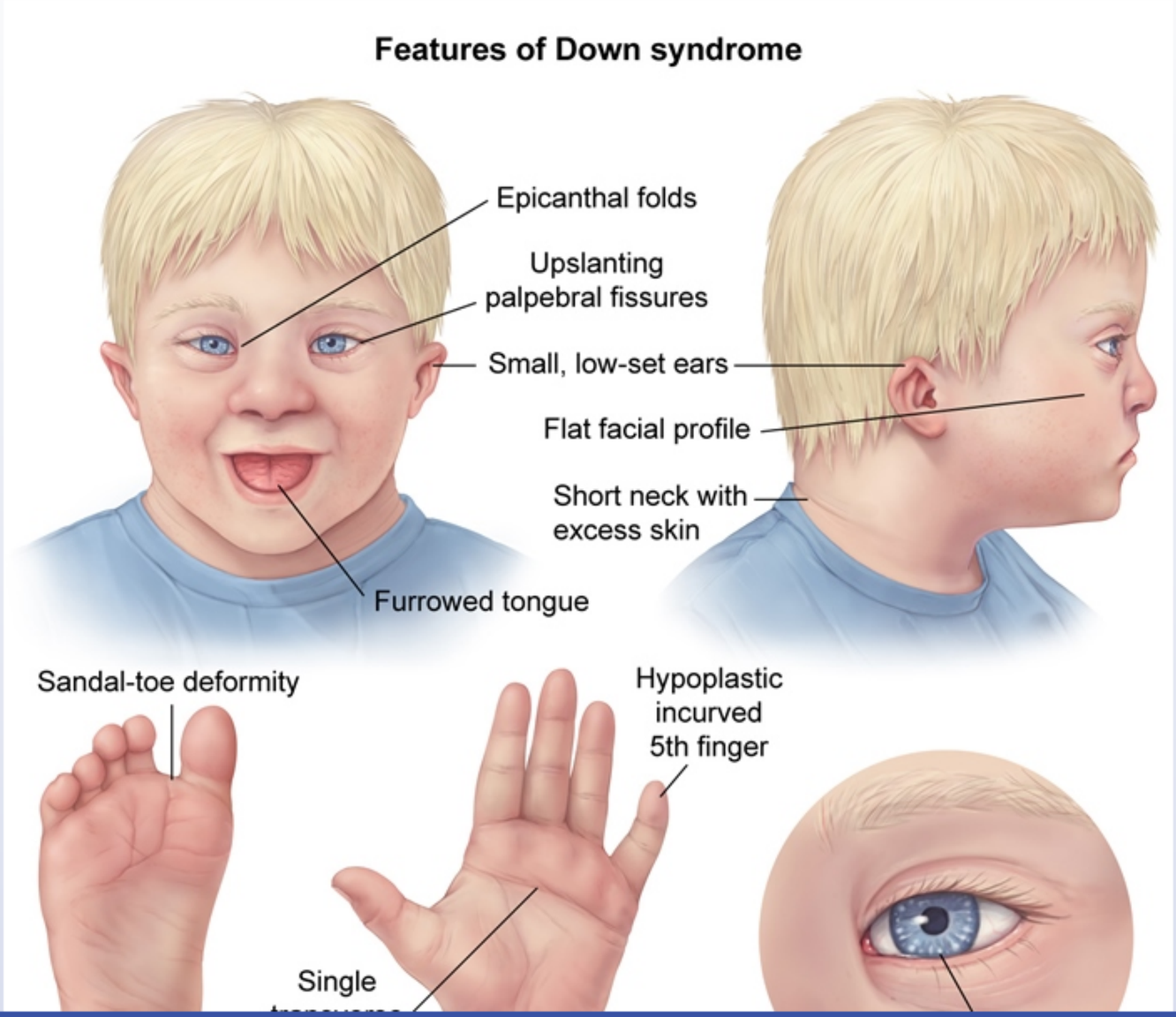

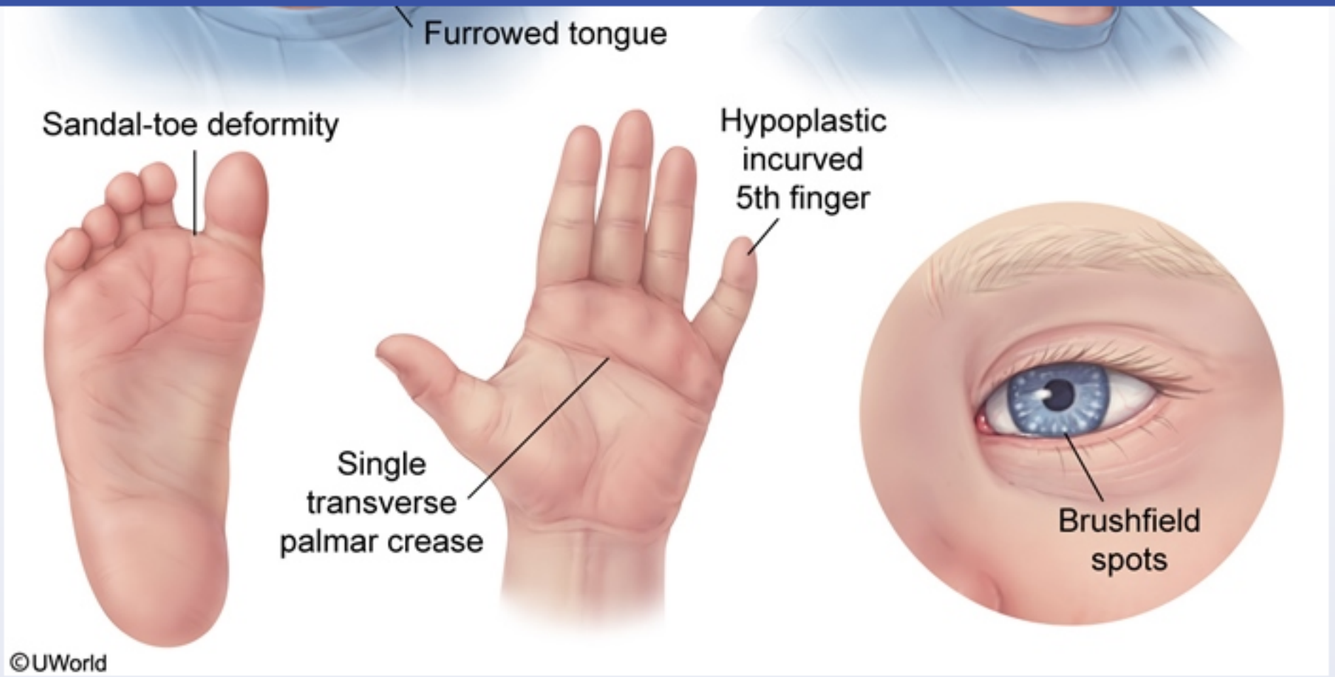

Down syndrome (trisomy 21) is the most common trisomy in liveborn infants. The diagnosis is often suspected by prenatal screening (eg, **decreased maternal serum alpha-fetoprotein** [AFP]) and/or ultrasonography (eg, **increased nuchal translucency**) and confirmed by chorionic villous sampling or amniocentesis. Most cases are caused by meiotic nondisjunction due to maternal age ≥35, which result in 3 complete copies of chromosome 21.

Duodenal atresia, the failure of recanalization of the duodenum in early gestation, is the most common gastrointestinal abnormality associated with Down syndrome. Infants present during the first few days of life with bilious emesis and the classic "double-bubble" sign, which represents the dilated stomach and proximal duodenum. Patients with Down syndrome are also at risk for imperforate anus, Hirschsprung disease, tracheoesophageal fistula, and celiac disease.

(Choice B) Holoprosencephaly, a severe developmental defect of the forebrain (prosencephalon), is associated with trisomy 13 (Patau syndrome). Additional features include microcephaly, microphthalmia, cleft lip/palate, and intellectual disability.

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(Choice B) Holoprosencephaly, a severe developmental defect of the forebrain (prosencephalon), is associated with trisomy 13 (Patau syndrome). Additional features include microcephaly, microphthalmia, cleft lip/palate, and intellectual disability.

(Choices C and E) Markedly elevated AFP levels are associated with open neural tube and ventral wall defects (omphalocele, gastroschisis). Myelomeningocele is associated with trisomy 18, and omphalocele is associated with trisomies 13 and 18.

(Choice D) Nephroblastoma, or Wilms tumor, typically presents before age 5 with an abdominal mass. The majority of cases are sporadic, but a subset is associated with Beckwith-Wiedemann syndrome.

(Choice F) Pyloric stenosis is caused by hypertrophy of the pylorus and presents at age 3-6 weeks with forceful, nonbilious emesis. Pyloric stenosis is not associated with Down syndrome.

Educational objective:
Down syndrome (trisomy 21) is associated with decreased maternal serum alpha-fetoprotein and increased nuchal translucency. Duodenal atresia is the most common gastrointestinal complication in these patients.

References

- Associated congenital anomalies among cases with Down syndrome.

Genetics	Miscellaneous (Multisystem)	Down syndrome
Subject	System	Topic

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Duodenal atresia, the failure of recanalization of the duodenum in early gestation, is the most common gastrointestinal abnormality associated with Down syndrome. Infants present during the first few days of life with bilious emesis and the classic "double-bubble" sign, which represents the dilated stomach and proximal duodenum. Patients with Down syndrome are also at risk for imperforate anus, Hirschsprung disease, tracheoesophageal fistula, and celiac disease.

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Subject	System	Topic

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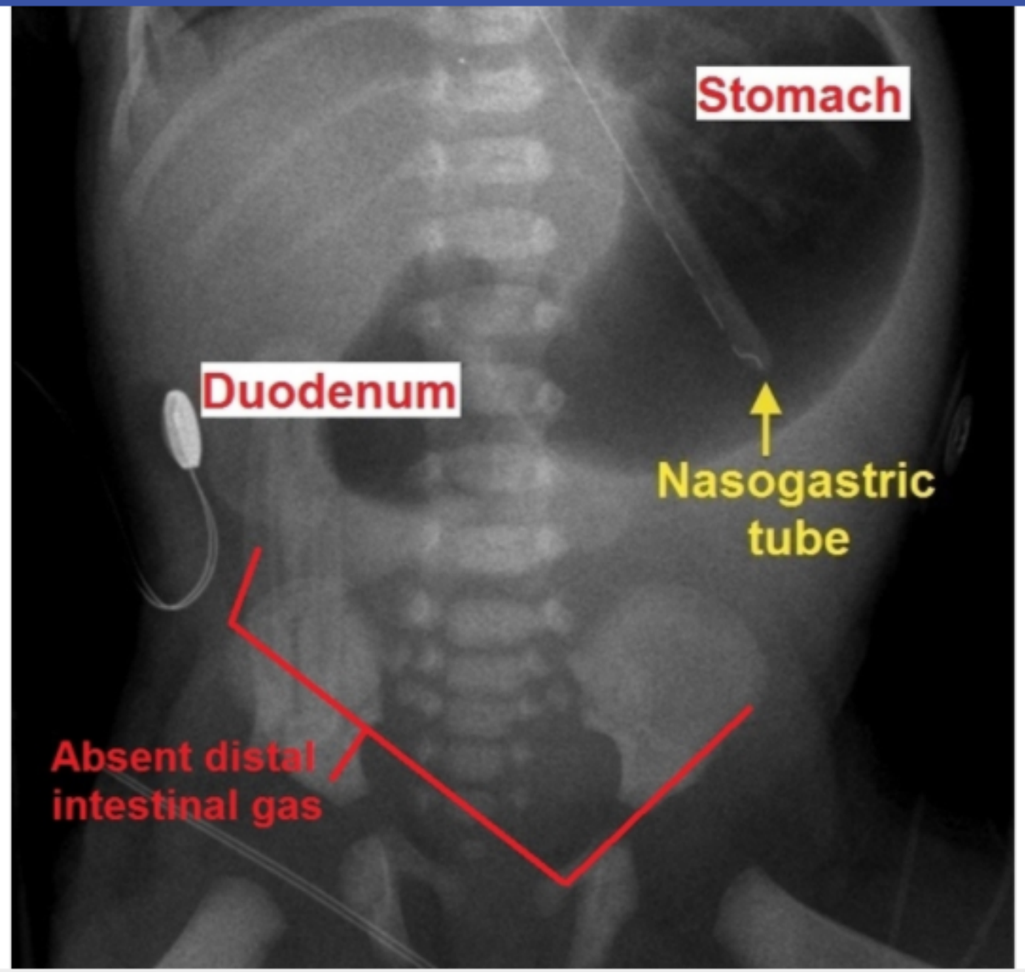

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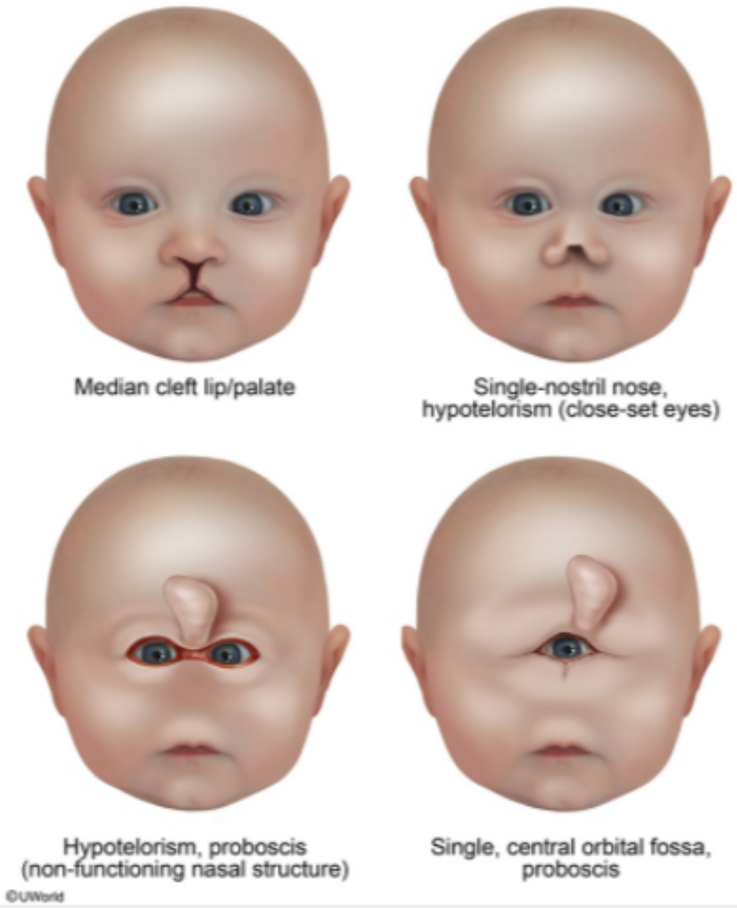
Holoprosencephaly spectrum



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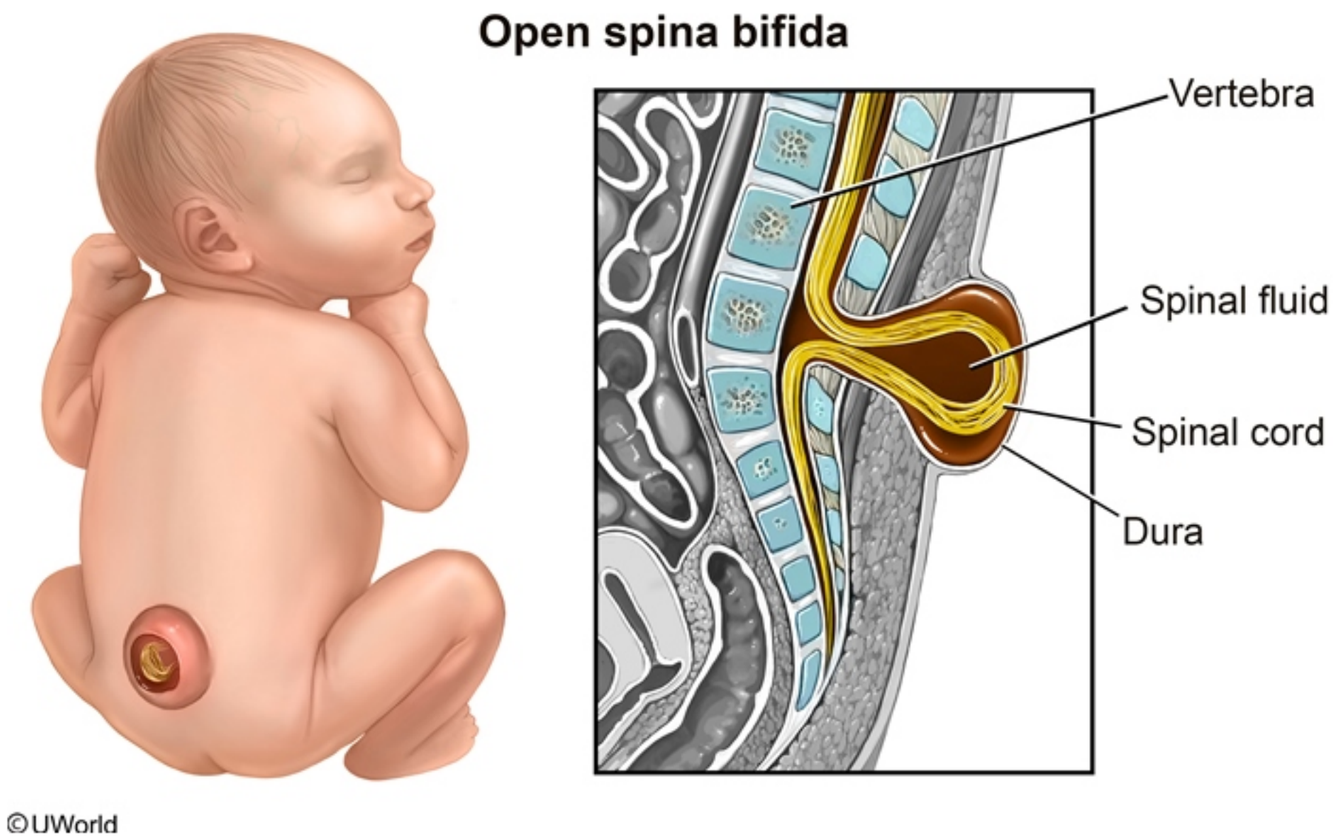

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villous sampling or amniocentesis. Most cases are caused by meiotic nondisjunction due to maternal age ≥36, which result in 3 complete copies of chromosome 21.

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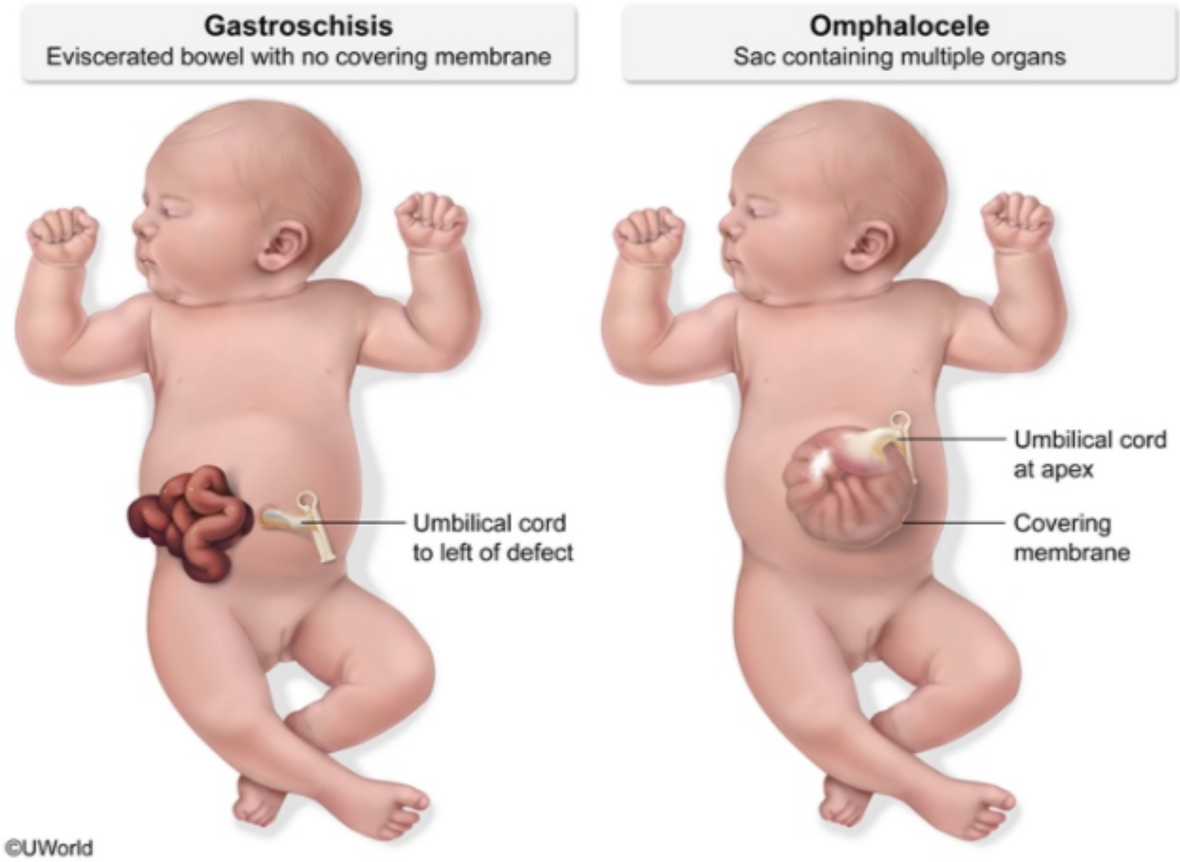
Gastroschisis vs. omphalocele



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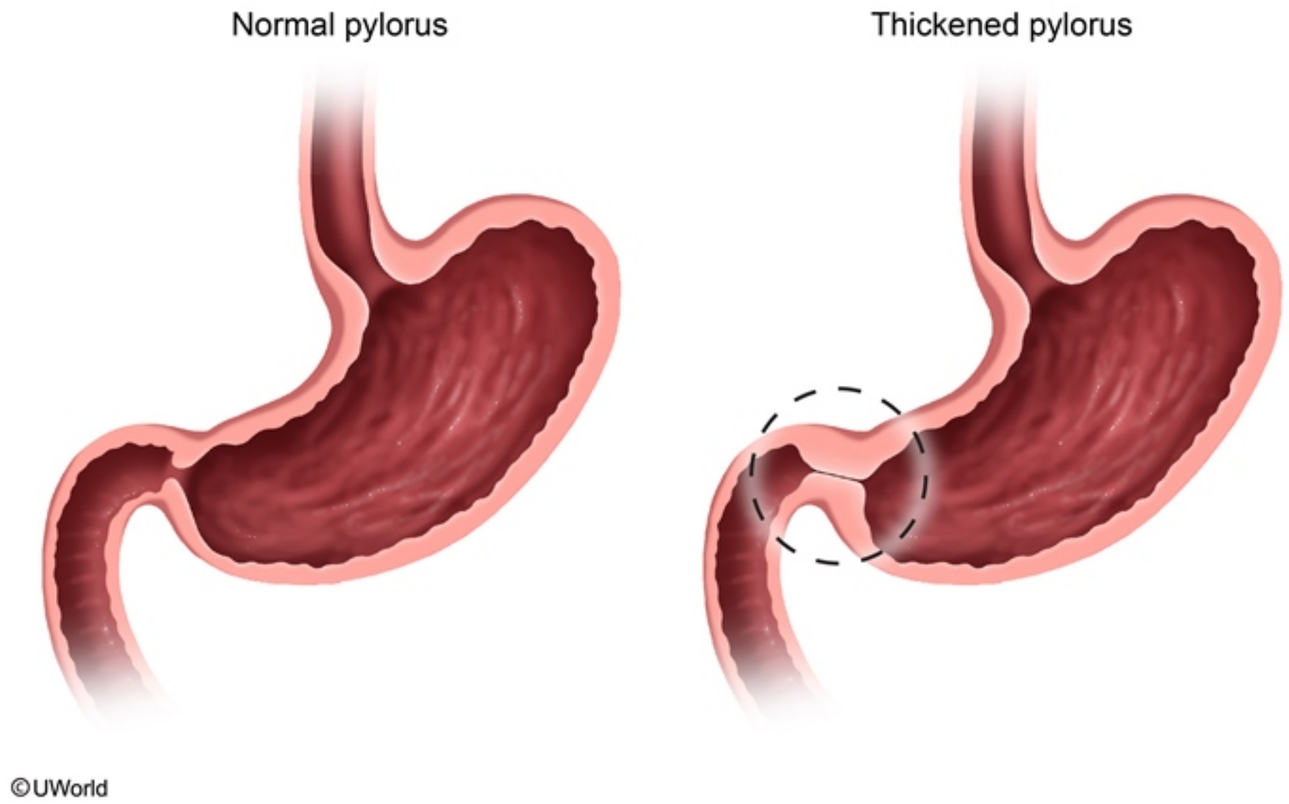
Hypertrophic pyloric stenosis



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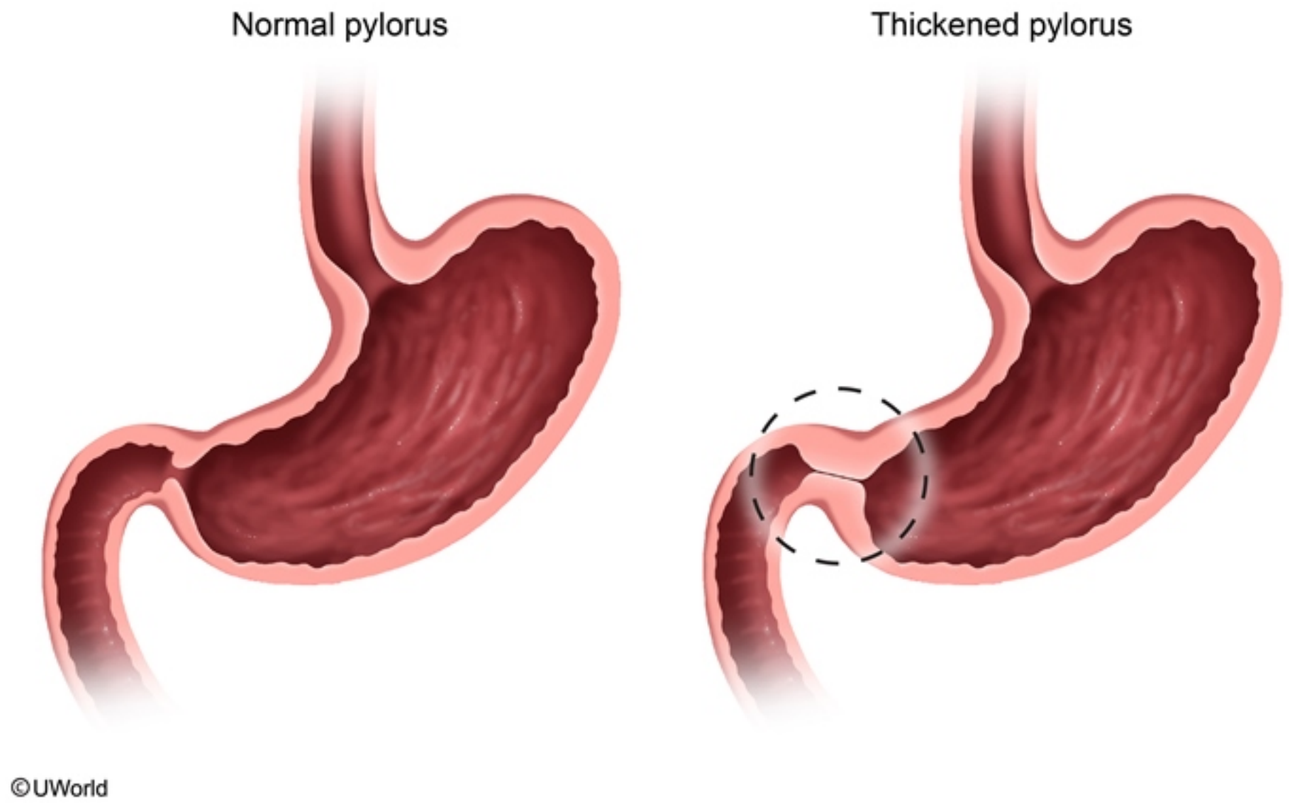

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Geneticists are studying a malfunctioning protein that causes impaired endothelial cell migration and angiogenesis. They have noticed that the amino acid sequence of the protein is truncated compared to normal controls. The mutated mRNA strand is isolated, and analysis shows a nonsense mutation located near the 3' end of the coding region. The 3' terminal coding sequence of the abnormal mRNA strand is shown below.

5'——ACG—CUA—CCA—UUG—UAA—CAA—GUU—AGC—UAG——3'

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Which of the following tRNA anticodons is responsible for adding the last amino acid to the truncated polypeptide during protein translation?

- A. 5'-AAC-3'
- B. 5'-AUC-3'
- C. 5'-CAA-3'
- D. 5'-GCU-3'
- E. 5'-UCG-3'

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Which of the following tRNA anticodons is responsible for adding the last amino acid to the truncated polypeptide during protein translation?

- A. 5'-AAC-3' (6%)
- B. 5'-AUC-3' (38%)
- ✓ C. 5'-CAA-3' (32%)
- D. 5'-GCU-3' (15%)
- E. 5'-UCG-3' (8%)

Omitted
Correct answer
C

32%
Answered correctly

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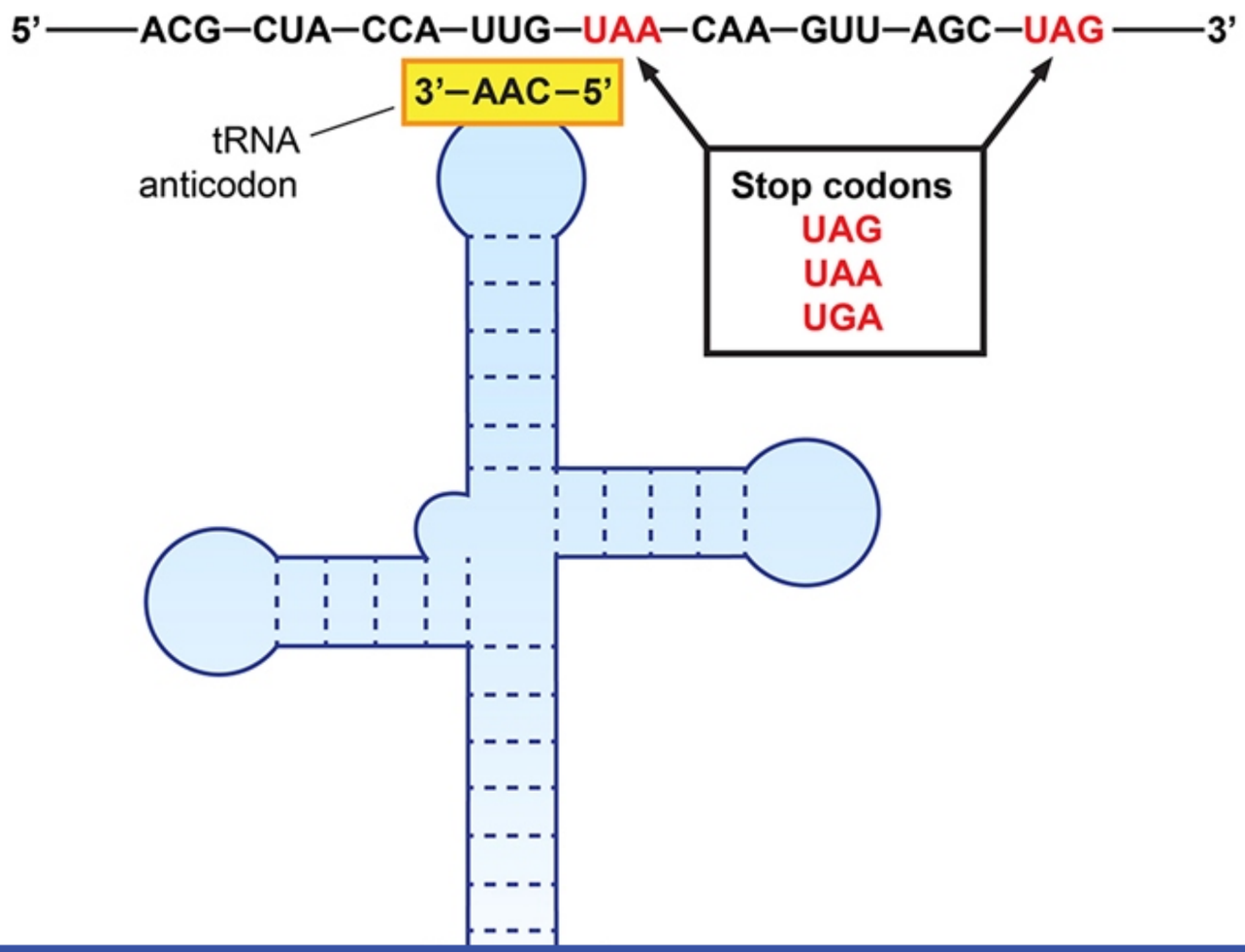
Explanation

mRNA, tRNA, & stop codons

mRNA, tRNA, & stop codons



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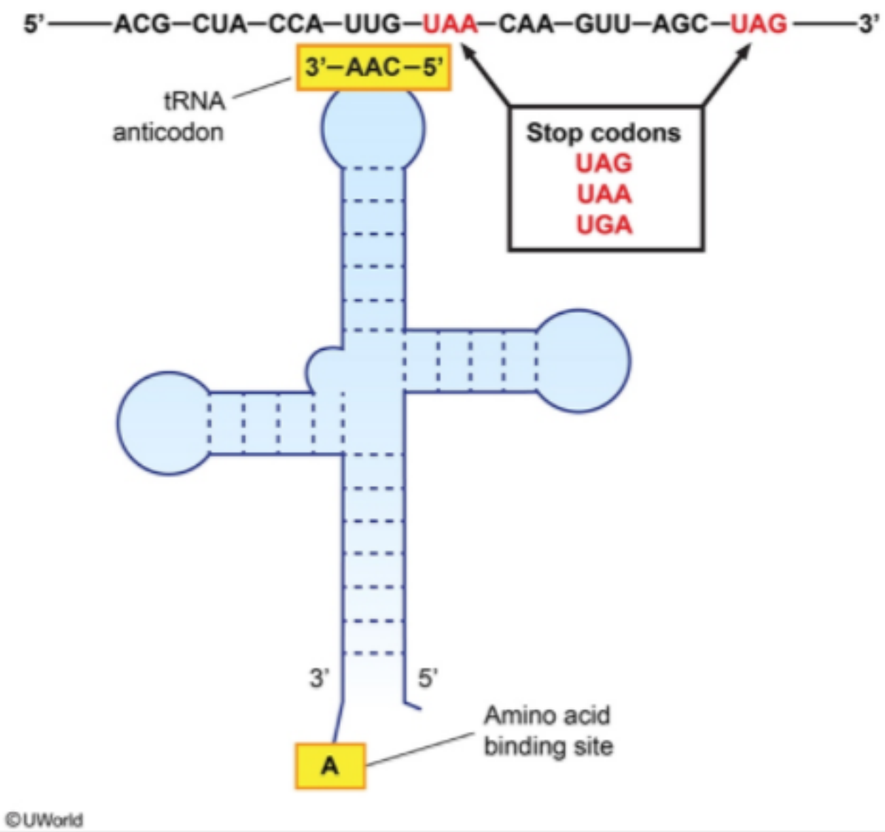
mRNA, tRNA, & stop codons



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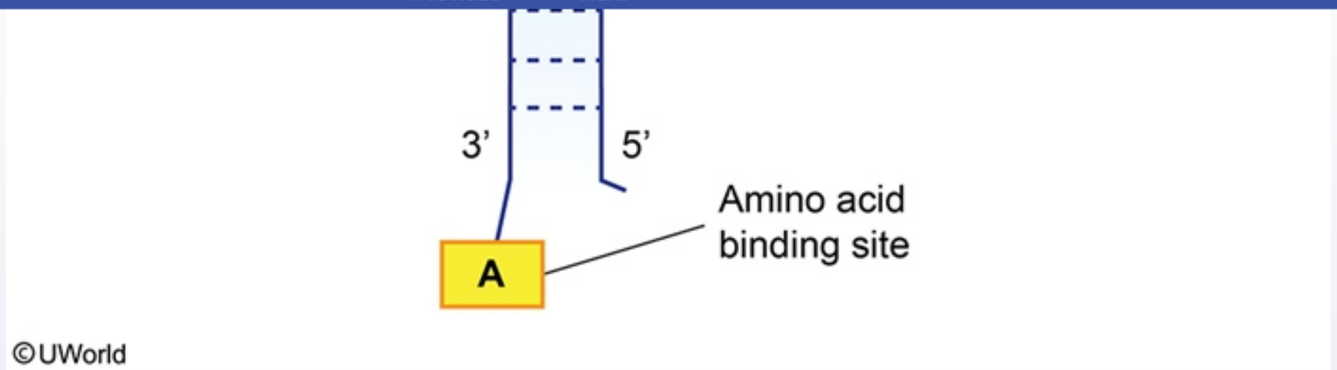

One codon (AUG) signals initiation of protein synthesis and 3 codons (**UAA**, **UAG**, and **UGA**) stop protein synthesis. **Stop codons** function only to terminate translation; they do not add amino acids to the polypeptide chain.

Transfer RNA molecules (**tRNA**) transport amino acids to the ribosome and ensure placement of the proper amino acid. One end of the molecule serves as the amino acid binding site; the opposite end contains a specific nucleic acid sequence known as the **anticodon** that is **complementary** to one or more **mRNA codons** (due to base wobbling). The type of amino acid that is bound to each tRNA molecule is determined by its anticodon sequence; this ensures that the proper amino acid is added at each mRNA codon during protein synthesis.

Translation of the mRNA template proceeds in the 5' to 3' direction. The mRNA of the dysfunctional protein in the question stem contains an extra stop codon (UAA) before the normal stop codon (UAG) at the end of the template. During protein translation, the **first stop codon** encountered will **bind a release factor**, halting protein synthesis. Therefore, the codon just prior to the first stop codon will be the last codon to add an amino acid. In this case, (**5'-UUG-3'**) is the last codon to add an amino acid to the truncated protein, and this amino acid will be carried by the **5'-CAA-3'** anticodon (codon-anticodon binding occurs in opposite directions [ie, **5' to 3' binds 3' to 5'**]).

(Choice A) Because complementary sequences align in antiparallel fashion, during translation the tRNA anticodons will bind the 5' to 3' mRNA in the (opposite) 3' to 5' direction. Therefore, the **5'**-UUG-**3'** mRNA codon will bind the **5'**-CAA-**3'** tRNA anticodon, not the **5'**-AAC-**3'** anticodon.

(Choices B and E) The 5'-AUC-3' and 5'-UCG-3' anticodons will bind to the 5'-GAU-3' and 5'-CGA-3' codons, respectively (5' to 3' binds 3' to 5'). These are not present in the above mRNA sequence.

(Choice D) The last codon shown in the above mRNA sequence is 5'-UAG-3' (a stop codon), with the second-to-last codon being 5'-AGC-3'.

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(Choice D) The last codon shown in the above mRNA sequence is 5'-UAG-3' (a stop codon), with the second-to-last codon being 5'-AGC-3'. Therefore, 5'-GCU-3' would be the tRNA anticodon responsible for adding the last amino acid to the normal (non-truncated) protein.

Educational objective:
Translation of the mRNA template proceeds in the 5' to 3' direction. Because complementary sequences align in antiparallel fashion, during translation tRNA anticodons will be oriented in the opposite 3' to 5' direction. Stop codons (UAA, UAG, and UGA) halt protein synthesis by binding a release factor; they do not add amino acids to the polypeptide chain.

Genetics	Miscellaneous (Multisystem)	Genetic code
Subject	System	Topic

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A pharmaceutical researcher develops a therapy to treat a protein misfolding disorder. Specifically, a mutation in this disorder leads to abnormal protein folding and subsequent intracellular degradation of the protein before it can reach the cell membrane. With the new combination drug therapy, the first drug corrects the processing and trafficking of the protein, enabling it to reach the cell surface membrane. Once the protein has reached the cell surface, its function is enhanced by the second drug. This therapy is most likely to be helpful in which of the following conditions?

A. Alzheimer disease

B. Creutzfeldt-Jakob disease

C. Cystic fibrosis

D. Phenylketonuria

E. Sickle cell anemia

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- A. Alzheimer disease (8%)
- B. Creutzfeldt-Jakob disease (9%)
- ✓ C. Cystic fibrosis (78%)
- D. Phenylketonuria (1%)
- E. Sickle cell anemia (1%)

Omitted
Correct answer
C

78%
Answered correctly

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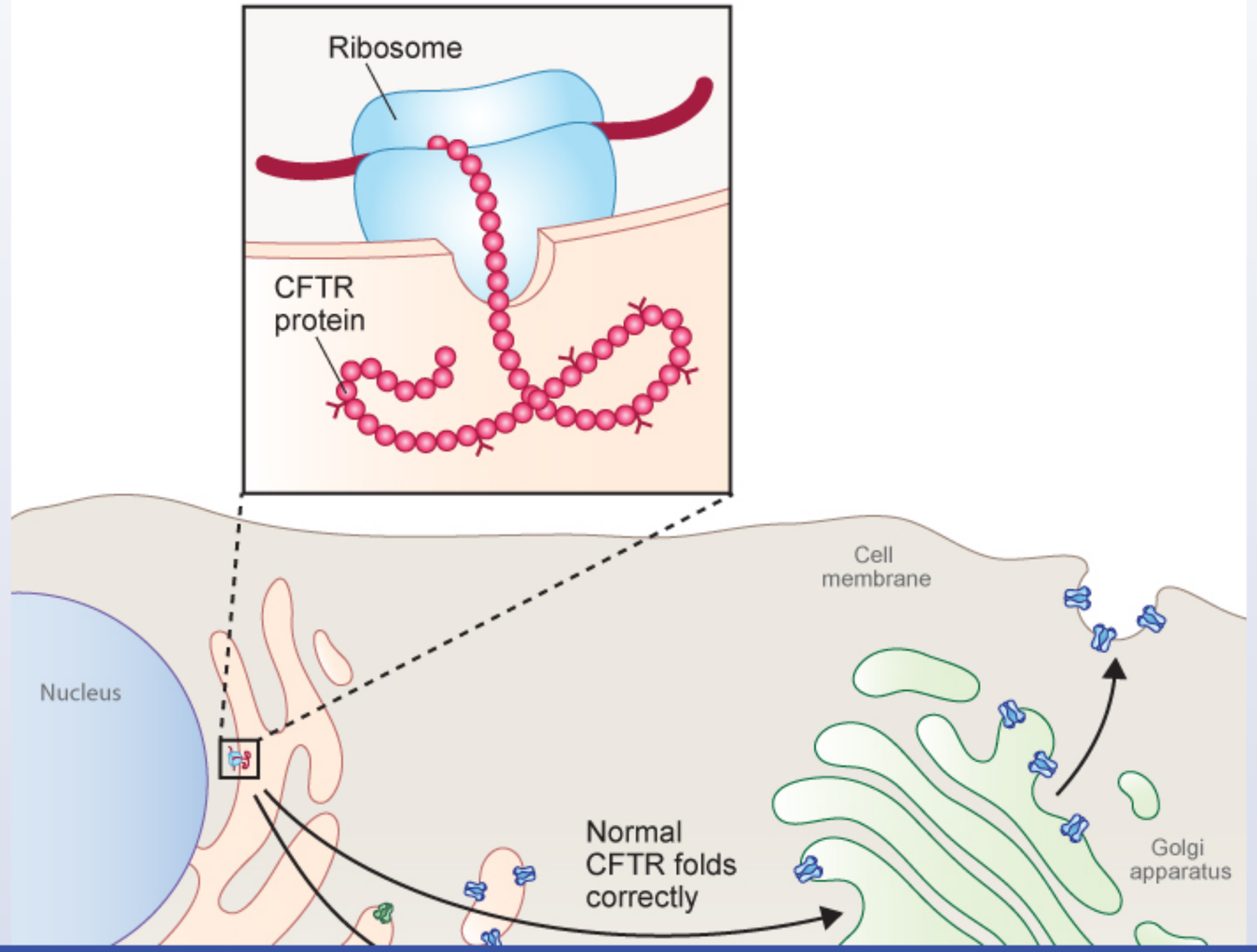
ΔF508 mutations & CFTR post-translational processing



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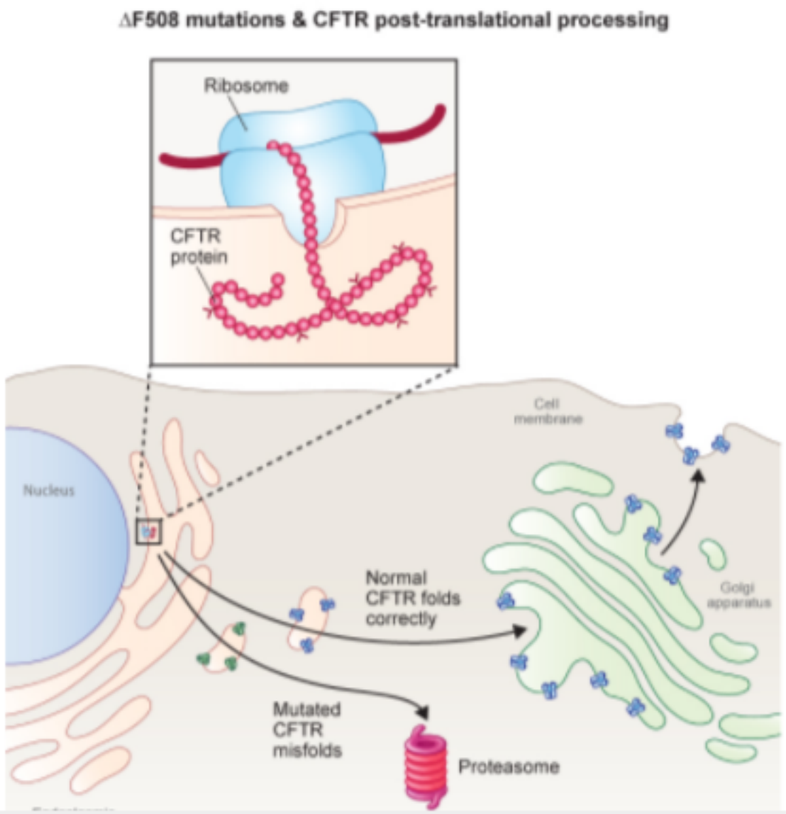

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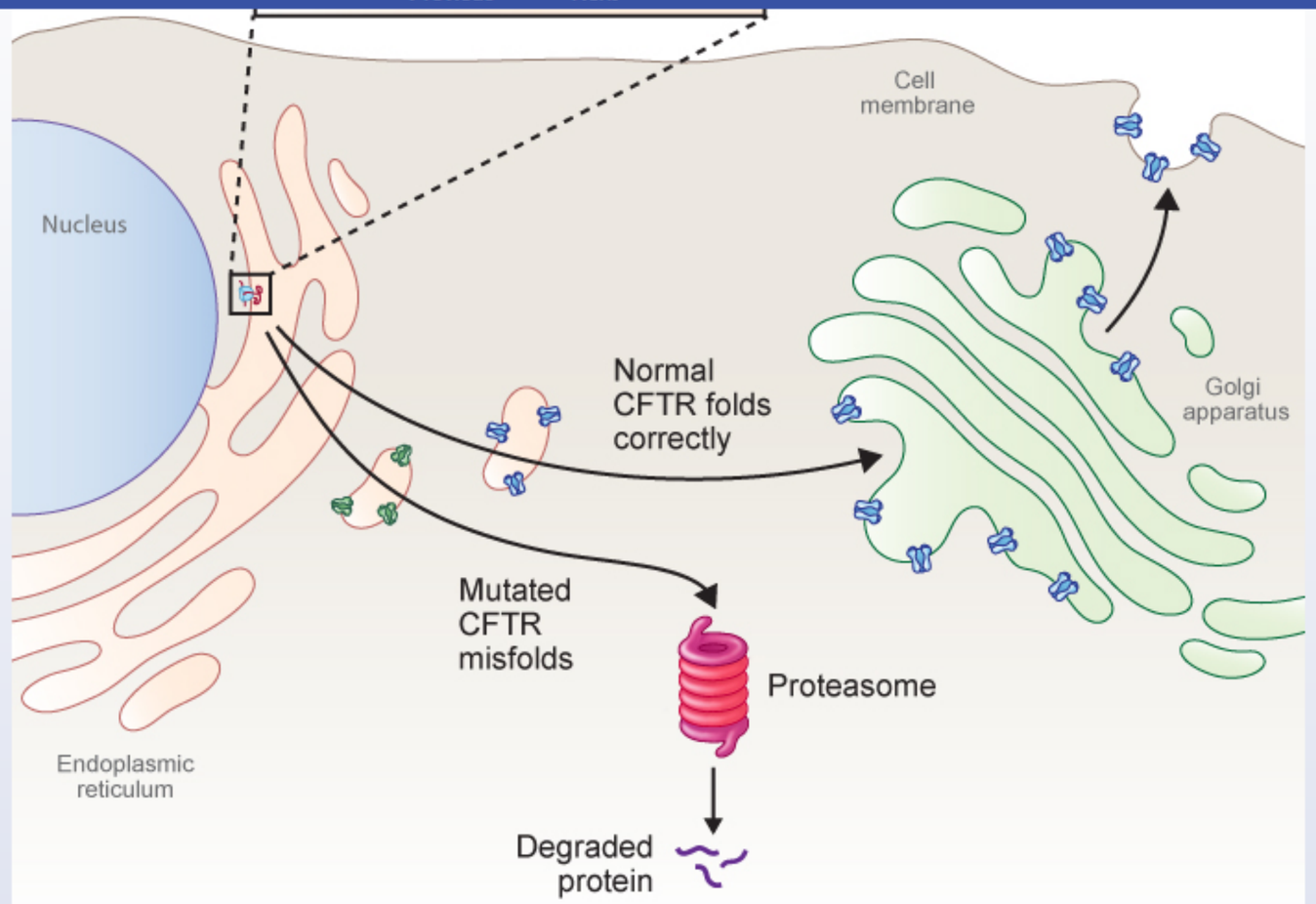

CFTR = cystic fibrosis transmembrane conductance regulator.
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Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane regulator (CFTR) protein. **ΔF508** is the most common CFTR gene mutation in patients with CF. This deletion causes **abnormal protein folding** and failure of glycosylation. The CFTR protein is then **targeted for degradation** by the proteasome before reaching the cell surface, causing an almost complete **absence from the apical membrane** of exocrine ductal epithelial cells. The rare CFTR proteins that do reach the cell membrane are abnormal, as the ΔF508 mutation also reduces

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Lumacaftor and ivacaftor are CFTR-modulating medications that can potentially help patients with CF by restoring CFTR proteins to the membrane and also by enhancing protein function (eg, chloride transport) at the membrane, respectively. The combination of these 2 medications in patients with homozygous ΔF508 mutations has been shown to improve predicted forced expiratory volume (FEV) and decrease rates of pulmonary exacerbations.

(Choice A) Polymorphisms in apolipoprotein E (APOE) are common in patients with Alzheimer disease (AD). The polymorphism leads to a conformational protein change that alters lipid binding, inhibits neurite growth, and leads to accumulation of amyloid-β, a peptide that aggregates in the brain in patients with AD. APOE is not a target of degradation or a transmembrane protein.

(Choice B) Creutzfeldt-Jakob disease is a neurodegenerative disease caused by prions, which are contagious pathogens comprised of small, misfolded proteins that induce abnormal folding of normal proteins. Aggregates of misfolded proteins are difficult to degrade and result in apoptosis and neuronal loss.

(Choice D) Phenylketonuria results from mutations in the hepatocyte enzyme phenylalanine hydroxylase. This enzyme is not normally transported to the cell surface.

(Choice E) Sickle cell anemia results from mutations in the β-globin gene, leading to production of hemoglobin S, which can polymerize in states of low oxygen content. Hemoglobin S is not a transmembrane protein.

Educational objective:
ΔF508 is the most common mutation in the cystic fibrosis transmembrane regulator (CFTR) protein in patients with cystic fibrosis. This mutation leads to protein misfolding and failure of glycosylation, followed by proteasome-mediated degradation and significantly decreased number of transmembrane CFTR proteins.

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(Choice E) Sickle cell anemia results from mutations in the β-globin gene, leading to production of hemoglobin S, which can polymerize in states of low oxygen content. Hemoglobin S is not a transmembrane protein.

Educational objective:
ΔF508 is the most common mutation in the cystic fibrosis transmembrane regulator (CFTR) protein in patients with cystic fibrosis. This mutation leads to protein misfolding and failure of glycosylation, followed by proteasome-mediated degradation and significantly decreased number of transmembrane CFTR proteins.

References

- Mechanisms of protein-folding diseases at a glance.
- Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR.
- Advances in the diagnosis and treatment of cystic fibrosis.

Genetics	Pulmonary & Critical Care	Cystic fibrosis
Subject	System	Topic

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A 26-year-old woman comes to the office for follow-up. The patient and her husband want to have a child, and she inquires about the risk of certain genetic conditions, including cystic fibrosis (CF). The patient is from a small city with a stable Caucasian population, where the carrier frequency for CF is 1/30 Caucasian individuals. Her husband is from a nearby community, where CF carrier frequency in individuals of Asian descent is 1/100. Both the patient, who is Caucasian, and her husband, who is of Asian descent, are healthy. What is the probability that a child born to a mother from the Caucasian community and a father from the Asian community will have the disease?

A. 1/900
B. 1/1,000
C. 1/3,000
D. 1/6,000
E. 1/12,000

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- A. 1/900 (3%)
- B. 1/1,000 (2%)
- C. 1/3,000 (29%)
- D. 1/6,000 (6%)
- ✓ E. 1/12,000 (58%)

Omitted
Correct answer
E

58%
Answered correctly

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Explanation

Autosomal recessive inheritance

Carrier parent (Aa)

A a

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Autosomal recessive inheritance

Carrier parent (Aa)

Carrier parent (Aa)	A	a
A	AA Normal child	Aa Carrier child
a	Aa Carrier child	aa Affected child

Offspring have 25% chance of being affected

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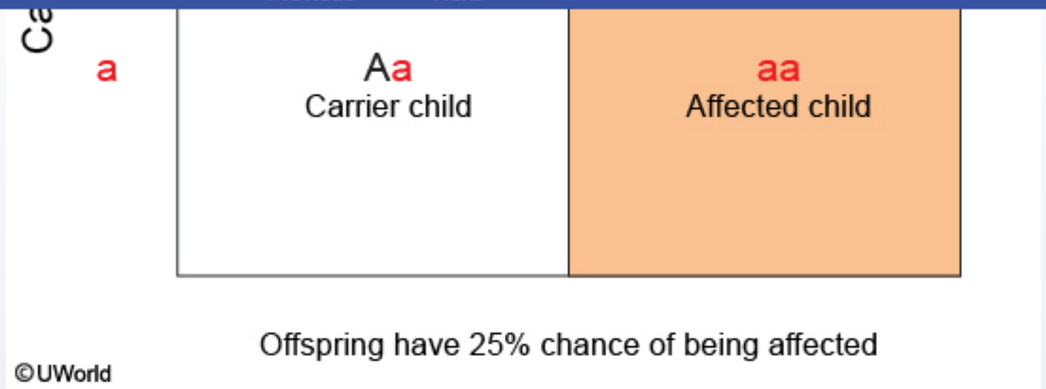
Cystic fibrosis (CF) is an **autosomal recessive** disease. The patient, who is Caucasian, has a 1/30 probability of carrying the mutant *CFTR* allele



Cystic fibrosis (CF) is an **autosomal recessive** disease. The patient, who is Caucasian, has a 1/30 probability of carrying the mutant *CFTR* allele and her husband, who is of Asian descent, has a 1/100 probability of carrying the same allele. If a parent is a **carrier**, the probability that the child will inherit the mutant allele from that parent is 1/2. However, to develop CF, the child must independently inherit a mutant allele from each parent (1/2 x 1/2 = **1/4** probability). Therefore:

P(affected child) = 1/4 x P(carrier mother) x P(carrier father) = 1/4 x 1/30 x 1/100 = 1/12,000.

An equivalent solution would be to state that the probability that the mother is a carrier and will transmit the mutant allele is (1/30 x 1/2) and the probability that the father is a carrier and will transmit the mutant allele is (1/100 x 1/2). The probability that both events will occur, producing a child with CF, is the product of the probabilities of these independent events = (1/30 x 1/2) x (1/100 x 1/2) = 1/12,000.

Educational objective:
The probability that a child of parents from 2 populations with different mutant allele carrier frequencies will inherit an autosomal recessive disease is 25% multiplied by the carrier frequencies.

Genetics	Pulmonary & Critical Care	Autosomal recessive inheritance
Subject	System	Topic

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A 58-year-old man comes to the office with a persistent dry cough. He has experienced an involuntary weight loss of 10 kg (22 lb) over the last 3 months. The patient drinks 2-3 beers daily and has a 40-pack-year smoking history. Physical examination shows dullness to percussion over the right lower lung base. A chest CT reveals a right-sided pleural effusion and a mass in the lower lobe of the right lung. Transbronchial biopsy of the mass demonstrates malignant cells with large nuclei that contain prominent, round, basophilic bodies as shown below.

Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

- A. DNA endonuclease
- B. DNA polymerase
- C. RNA polymerase I
- D. RNA polymerase II
- E. RNA polymerase III

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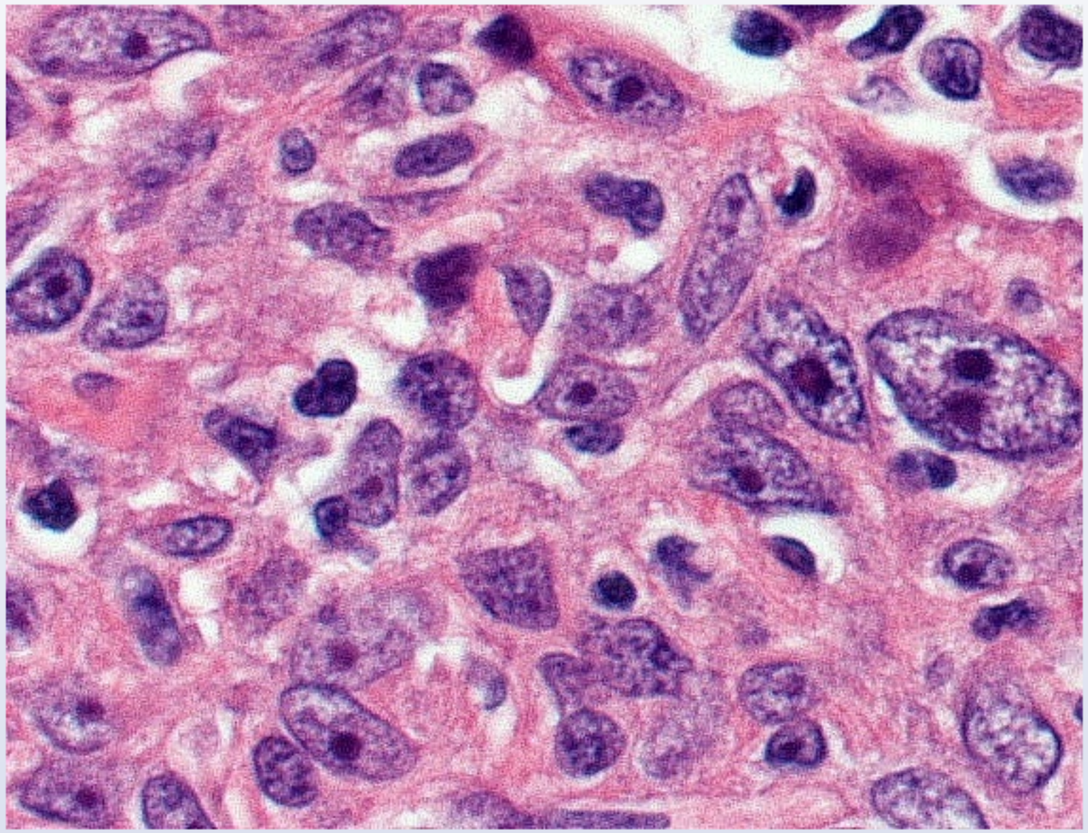

Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

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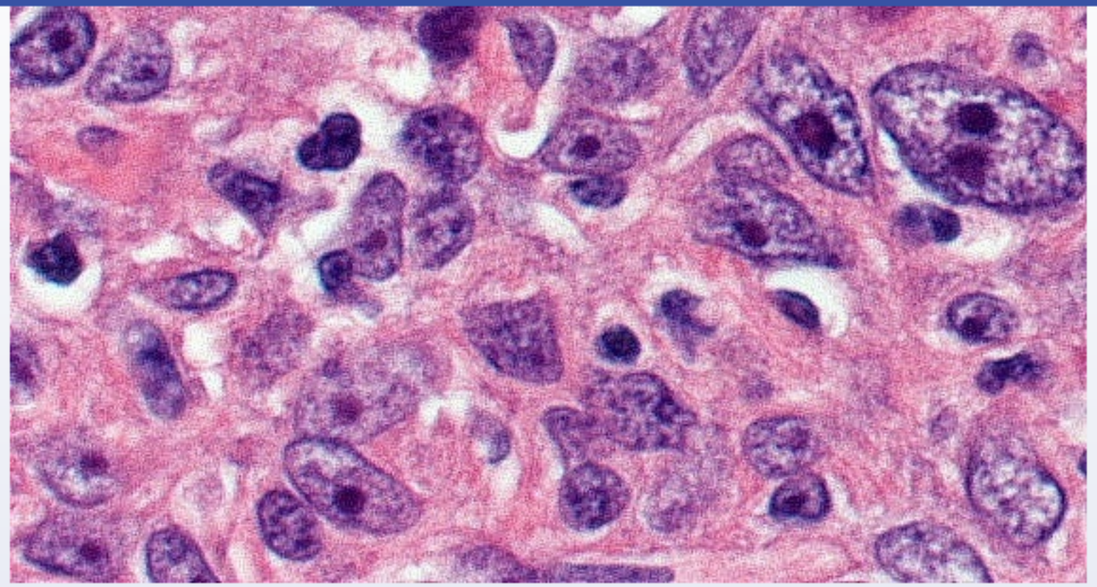

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- A. DNA endonuclease
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- C. RNA polymerase I
- D. RNA polymerase II
- E. RNA polymerase III

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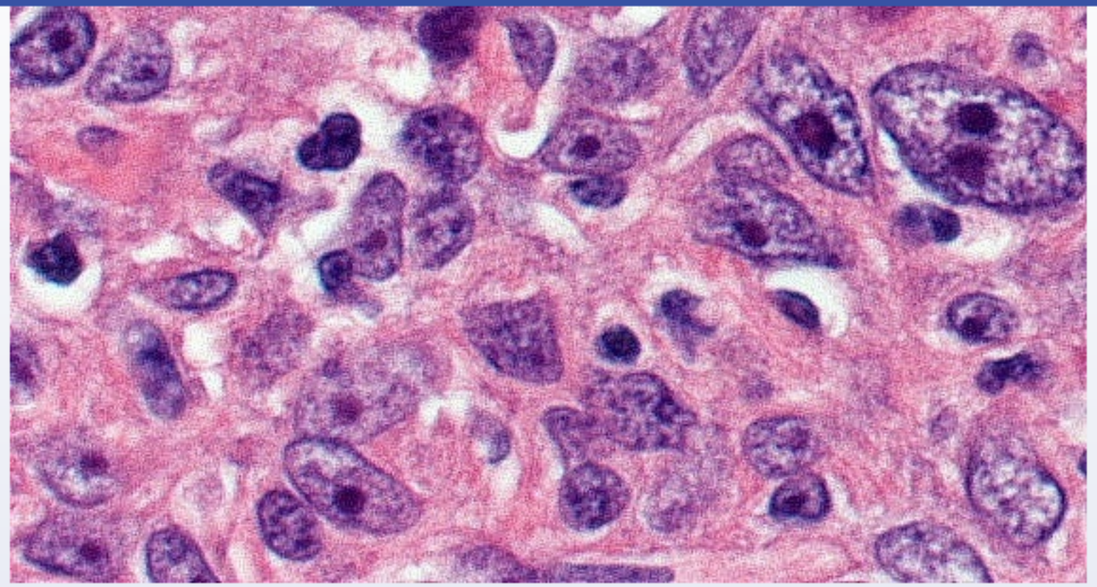

Which of the following enzymes is most likely to function only within this basophilic region of the nucleus?

- A. DNA endonuclease (11%)
- B. DNA polymerase (27%)
- ✓ C. RNA polymerase I (34%)
- D. RNA polymerase II (18%)
- E. RNA polymerase III (7%)

Omitted
Correct answer

34%
Answered correctly

06 secs
Time Spent

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Last Updated

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Synthesis & function of eukaryotic RNA

Synthesizing polymerase	Type of RNA produced	Function
RNA polymerase I	18S, 5.8S & 28S ribosomal RNA	Form essential ribosomal components
RNA polymerase II	Messenger RNA	Translated by ribosomes to form specific proteins
	Small nuclear RNA	Involved in mRNA splicing & transcription regulation
	Micro RNA	Cause gene silencing via translation arrest or mRNA degradation
RNA polymerase III	Transfer RNA	Adaptor molecule linking codons with specific amino acids
	5S ribosomal RNA	Essential component of 60S ribosomal subunit

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The **nucleolus** is a round, dense, basophilic (dark-staining) body that can be identified within the nucleus on standard light microscopy. It is the

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The **nucleolus** is a round, dense, basophilic (dark-staining) body that can be identified within the nucleus on standard light microscopy. It is the primary site of ribosomal RNA (rRNA) transcription. Although there are several hundred copies of the 45S pre-rRNA gene divided among multiple chromosomes, these are arranged into clusters called nucleolar organizing regions that position themselves so that all copies are located within the nucleolus. **RNA polymerase I** functions exclusively to transcribe the **45S pre-rRNA** gene into a single template that is subsequently processed into mature **18S**, **5.8S**, and **28S rRNAs**. As such, the function of RNA polymerase I is restricted to the nucleolus.

In addition to transcribing rRNA, the nucleolus is also involved in the maturation and assembly of ribosomal subunits. Ribosomal protein components are synthesized in the cytoplasm and transported into the nucleolus, where they combine with rRNA to form immature 40S and 60S subunits that are then shuttled out of the nucleus via nuclear pores. Regulation of ribosomal synthesis occurs in part by controlling the number of active rRNA genes. Generally, as cells become more differentiated, their growth slows and they require fewer numbers of ribosomes for protein production. In contrast, **malignant cells** with high metabolic activity usually have a large number of active rRNA genes and prominent nucleoli.

(Choice A) Endonucleases break the phosphodiester bond within the nucleotide chain in DNA and RNA. They are important in DNA repair and RNA splicing and are present throughout the nucleoplasm.

(Choice B) DNA polymerases are the primary enzymes responsible for DNA replication and repair. They are found throughout the nucleus.

(Choice D) RNA polymerase II synthesizes messenger RNA (mRNA), small nuclear RNA (snRNA), and micro RNA (miRNA). It is the most highly regulated of the 3 RNA polymerases, with its function determined by multiple transcription factors and regulatory processes.

(Choice E) RNA polymerase III transcribes DNA to form small RNA molecules such as transfer RNA (tRNA) and 5S rRNA. Unlike other rRNA molecules, the genes for the 5S rRNA are located outside the nucleolus.

Educational objective:
The nucleolus is the site of ribosomal subunit maturation and assembly. RNA polymerase I functions exclusively within the nucleolus to transcribe the 45S pre-rRNA gene, which codes for most of the ribosomal RNA components (18S, 5.8S, and 28S rRNAs).

References

- What the nucleolus says to a tumour pathologist.

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A patient is suspected of having an inherited disorder. Pedigree analysis shows the following pattern:

This patient most likely has which of the following conditions?

A. Classic galactosemia

B. Hemophilia B

C. Huntington disease

D. Leber hereditary optic neuropathy

E. Rett syndrome

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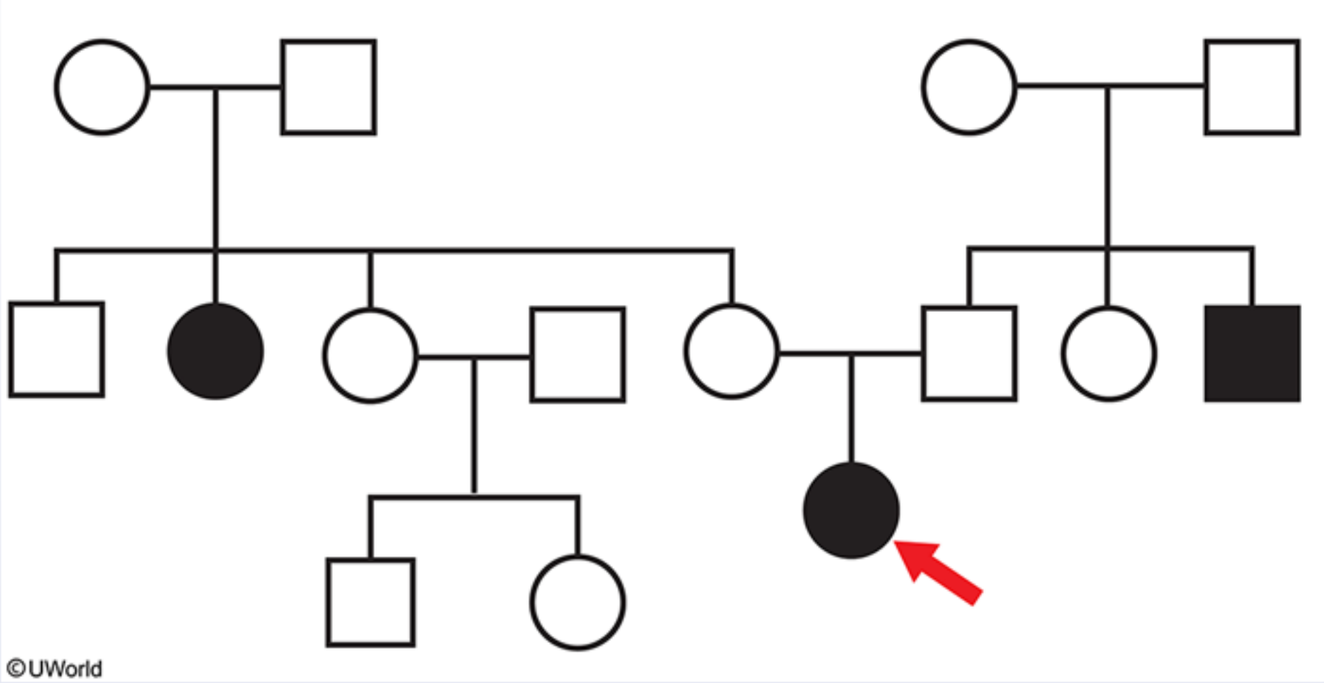

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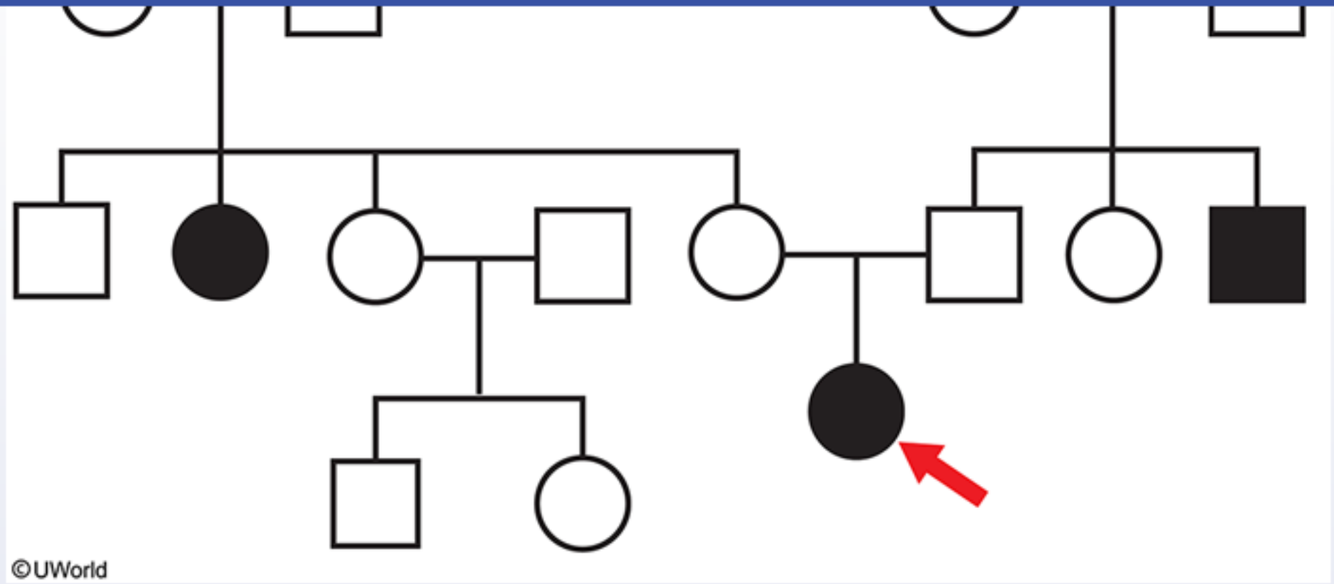

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- C. Huntington disease
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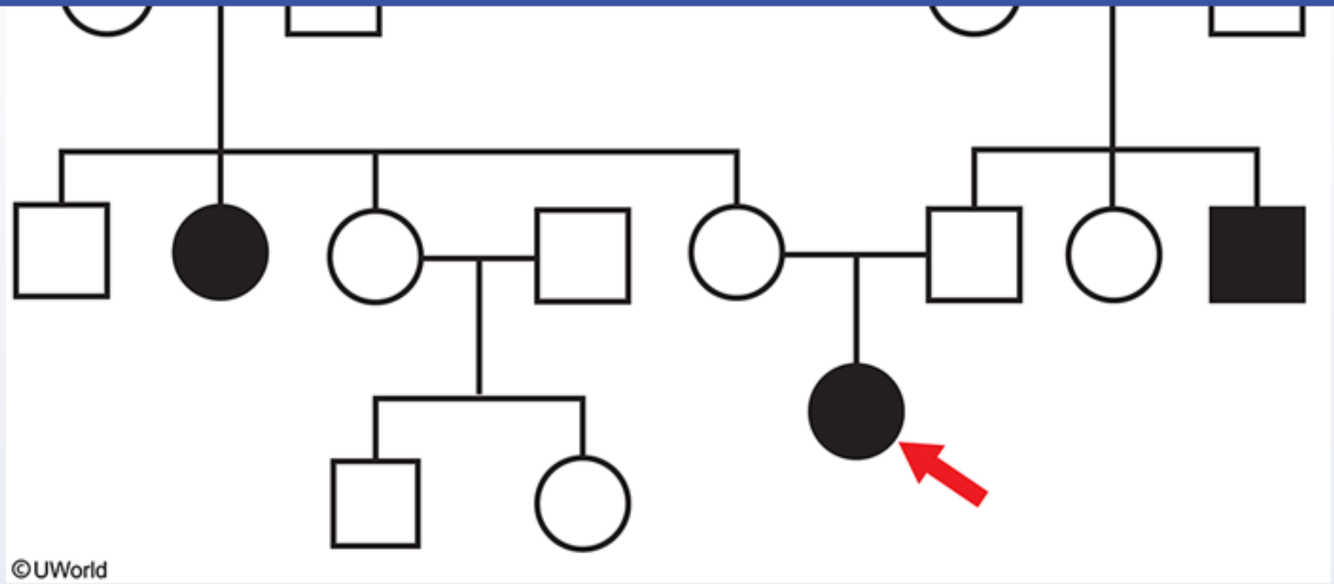

This patient most likely has which of the following conditions?

- A. Classic galactosemia (64%)
- B. Hemophilia B (16%)
- C. Huntington disease (6%)
- D. Leber hereditary optic neuropathy (6%)
- E. Rett syndrome (6%)

Omitted
Correct answer

64%
Answered correctly

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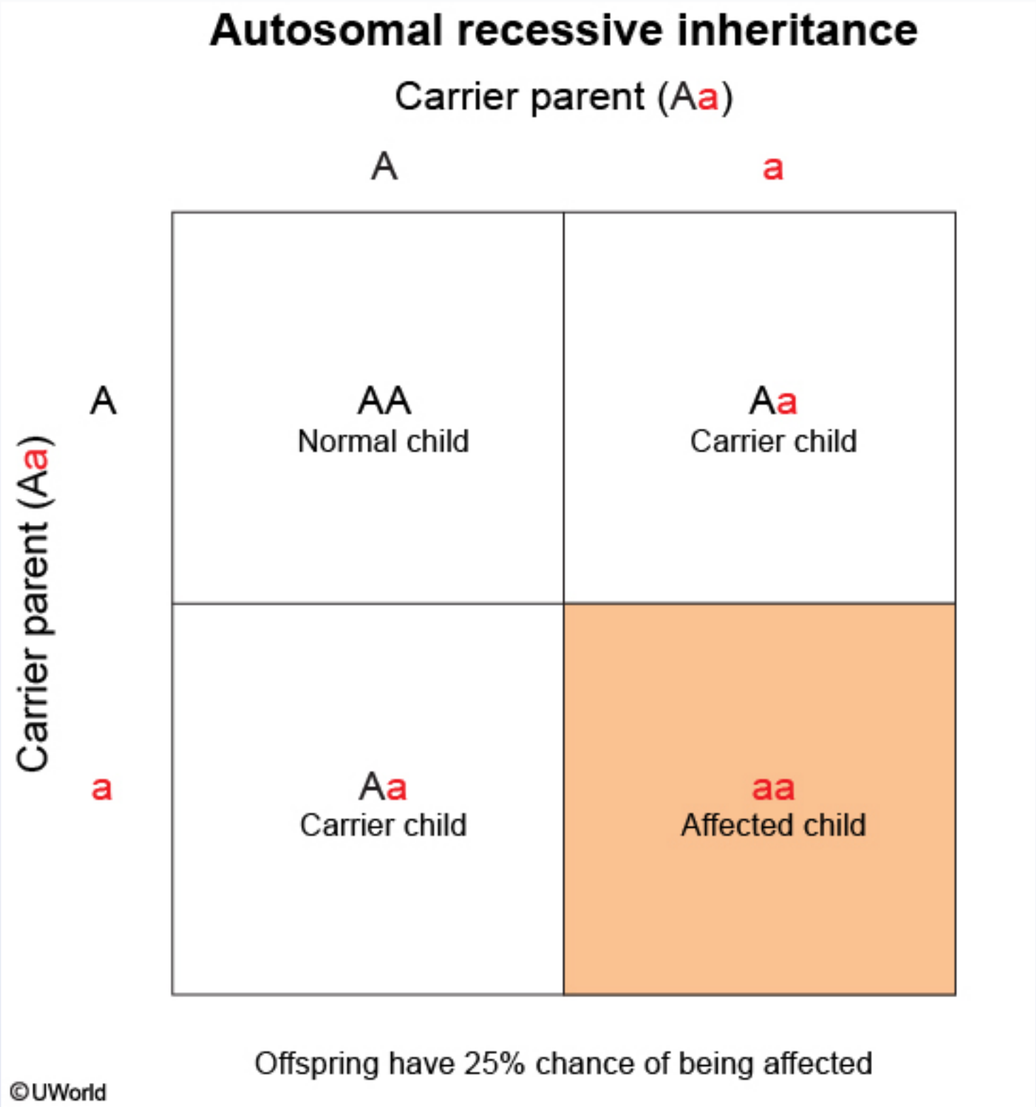

Each of the affected individuals on this pedigree inherited the disorder from **asymptomatic carrier parents**, which is consistent with a recessive

Each of the affected individuals on this pedigree inherited the disorder from **asymptomatic carrier parents**, which is consistent with a recessive inheritance pattern. Because **both males and females** inherit the condition, it is an **autosomal recessive** disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

Classic galactosemia is the most common and most severe of the galactosemic disorders. It is an autosomal recessive disorder leading to complete enzymatic absence of galactose-1-phosphate uridyl transferase. Newborns present within days of birth with jaundice, vomiting, and hepatomegaly.

In general, most **enzyme deficiency conditions** follow an autosomal recessive inheritance pattern whereas diseases due to defective noncatalytic proteins follow an autosomal dominant pattern.

(Choice B) Hemophilia B (Christmas disease) is an X-linked recessive disorder affecting **males** that causes factor IX deficiency with easy bruising and bleeding (eg, hemarthrosis, oral bleeding, intracranial hemorrhage). Affected males will have asymptomatic carrier mothers.

(Choice C) Huntington disease is an autosomal dominant disorder affecting males and females equally. It causes progressive neurodegeneration of the caudate and putamen, leading to chorea, dementia, and death. Patients usually have an affected parent.

(Choice D) Leber hereditary optic neuropathy is a mitochondrial inheritance disorder affecting all offspring of an affected mother; there is no father-child transmission. It is characterized by progressive bilateral optic neuropathy leading to blindness.

(Choice E) Rett syndrome is an X-linked dominant disorder affecting females (affected males die in utero) that presents in early childhood with progressive neurodegeneration and stereotypical hand movements. X-linked dominant conditions are characterized by a lack of father-son transmission whereas all daughters of an affected father are affected. Half of all offspring of an affected mother are also affected.

Educational objective:
Autosomal recessive disorders affect 25% of offspring of asymptomatic heterozygous carrier parents. Classical galactosemia is the most common and severe galactosemic disorder and presents within days of birth with jaundice, vomiting, and hepatomegaly.

Genetics	Miscellaneous (Multisystem)	Autosomal recessive inheritance
Subject	System	Topic

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inheritance pattern. Because both males and females inherit the condition, it is an autosomal recessive disorder. Based on this inheritance pattern, 50% of offspring will be asymptomatic carriers, 25% will be unaffected, and 25% will express the disorder.

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Genetics	Miscellaneous (Multisystem)	Autosomal recessive inheritance
Subject	System	Topic

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Exhibit Display

X-linked recessive inheritance Pedigrees- Stem

X-linked recessive inheritance

Affected father

Father \ Mother	X	X
Xd	XXd	XXd
Y	XY	XY

All daughters are carriers

All sons are normal

Carrier mother

Father \ Mother	X	Xd
X	XX	XXd
Y	XY	XdY

Daughters have 50% chance of becoming carriers

Sons have 50% chance of being affected

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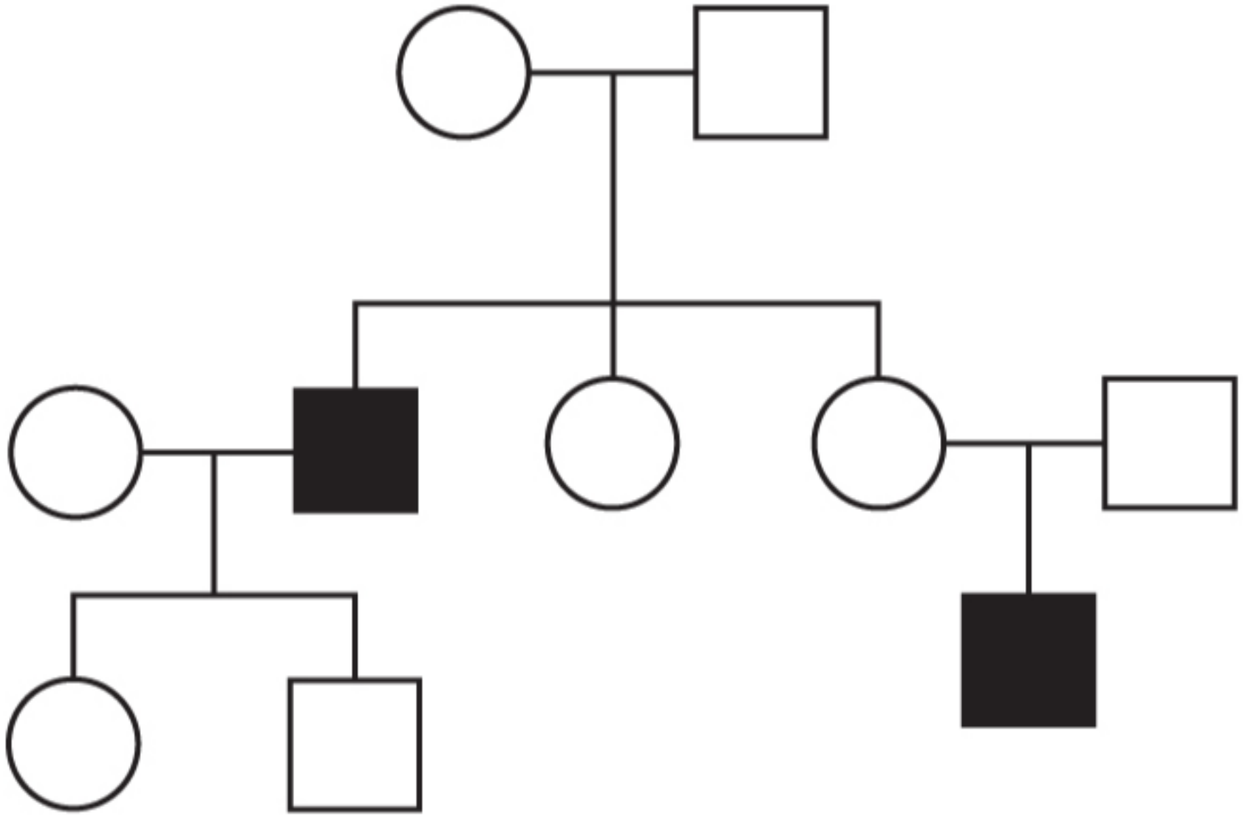
X-linked recessive inheritance Pedigrees- Stem



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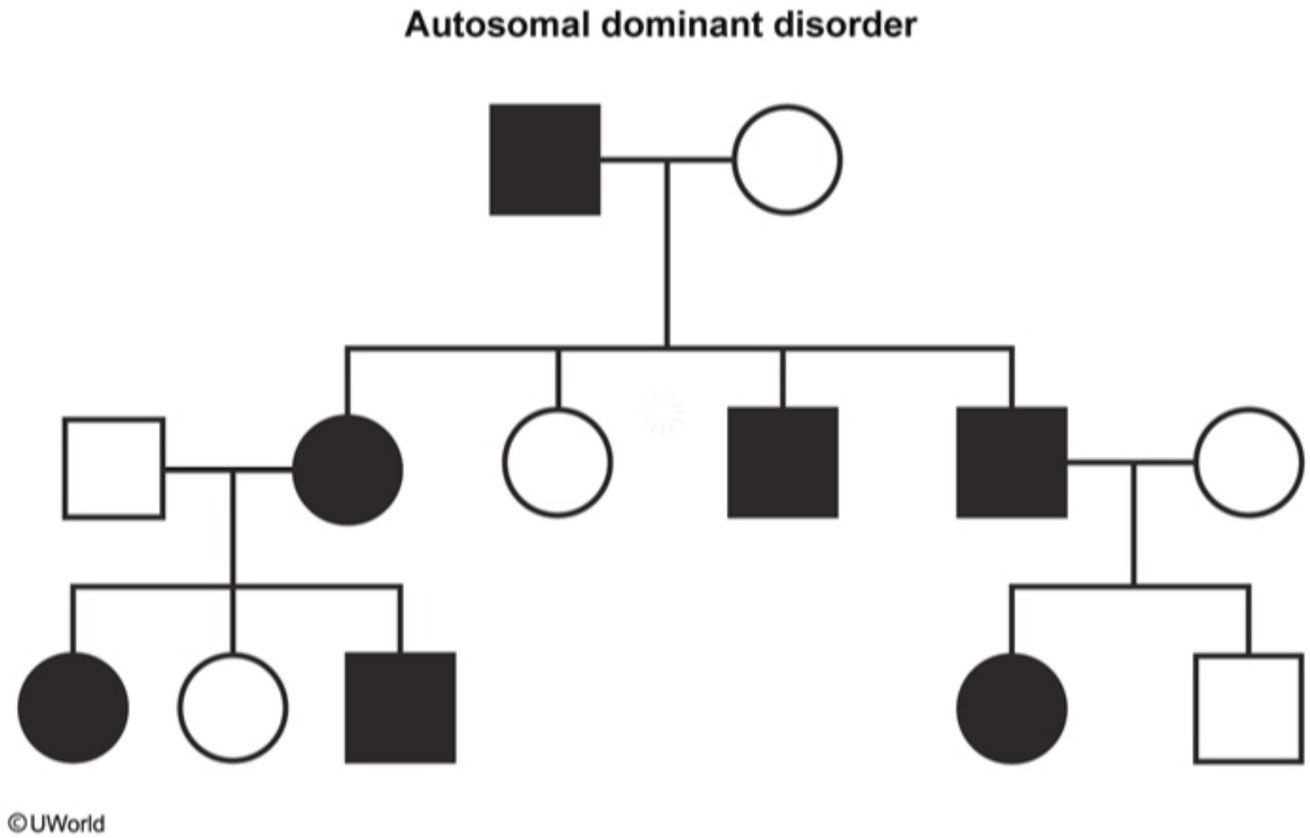

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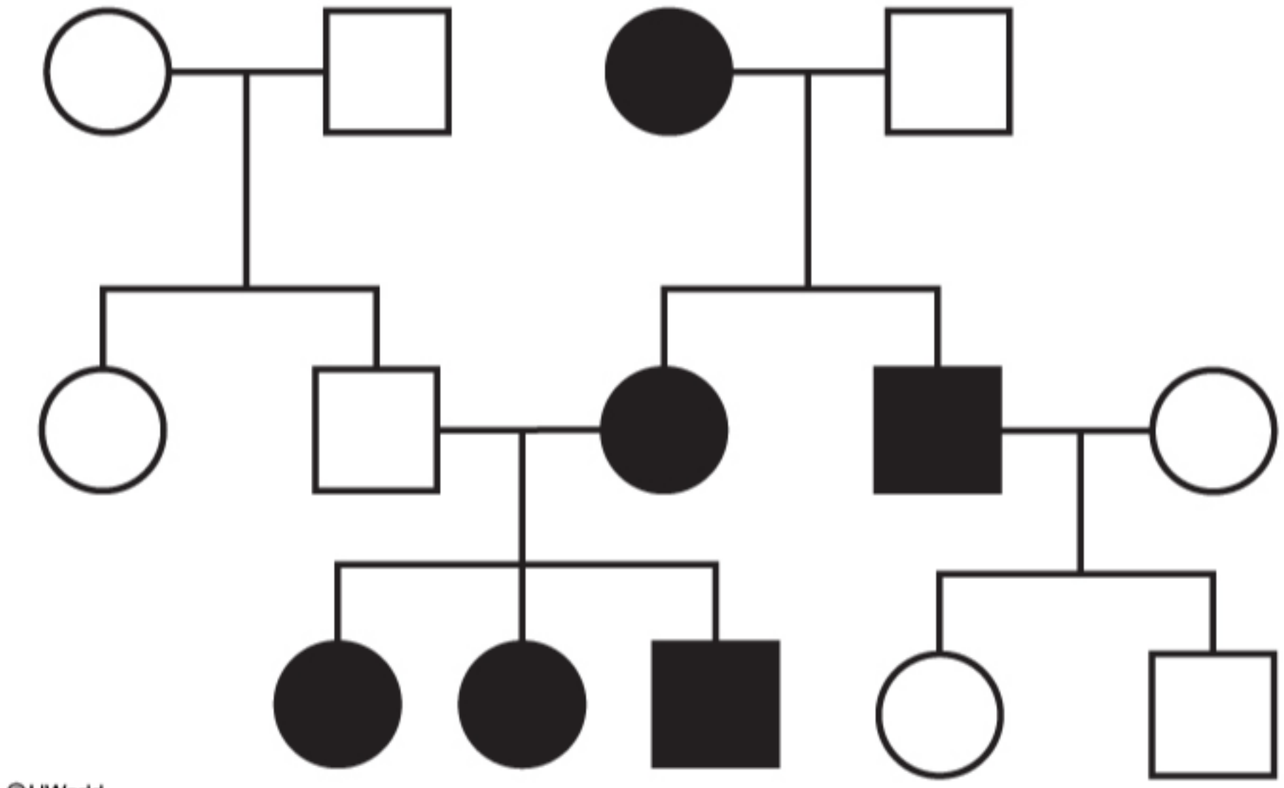
Mitochondrial inheritance disorder



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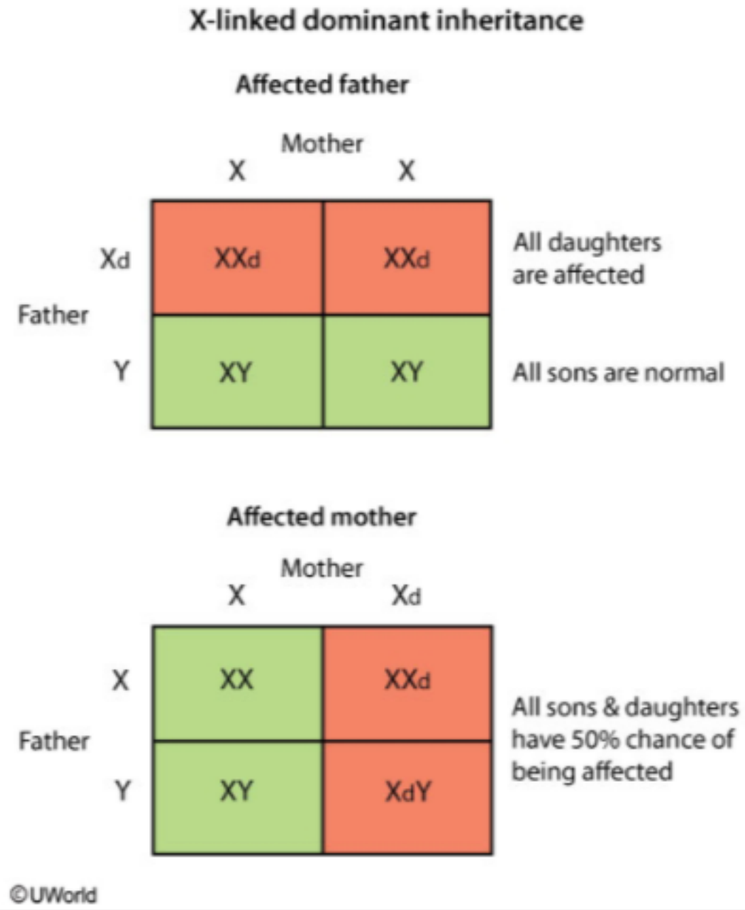
X-linked Dominant Inheritance Pedigrees- Stem



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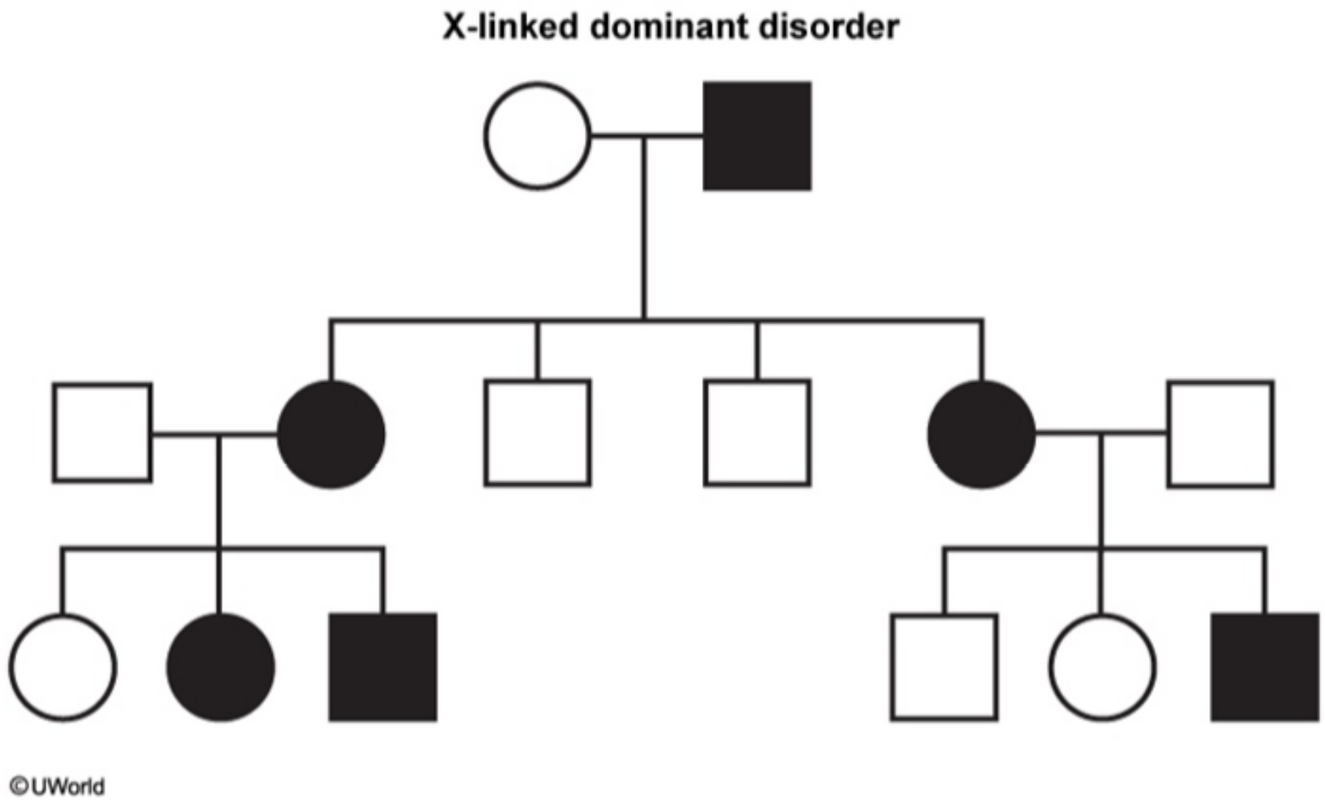
X-linked Dominant Inheritance Pedigrees- Stem



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A small-for-gestational-age infant is born prematurely to a 38-year-old woman who had inconsistent prenatal care. Physical examination shows a small head and eyes as well as a cleft lip and palate. There is a small, round punched-out lesion with an overlying thin membrane on the patient's scalp. A small, membranous sac with a loop of bowel protrudes from the patient's abdominal midline. The infant is transferred to the neonatal intensive care unit for further workup and management. Which of the following is most likely responsible for this patient's condition?

A. Down syndrome
B. Edwards syndrome
C. Maternal nicotine use
D. Maternal phenytoin ingestion
E. Maternal rubella infection
F. Patau syndrome
G. Williams syndrome

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A. Down syndrome (5%)
B. Edwards syndrome (11%)
C. Maternal nicotine use (4%)
D. Maternal phenytoin ingestion (15%)
E. Maternal rubella infection (3%)
✓ F. Patau syndrome (57%)
G. Williams syndrome (2%)

Omitted
Correct answer
F

57%
Answered correctly

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Explanation

Trisomy 13 (Patau syndrome)

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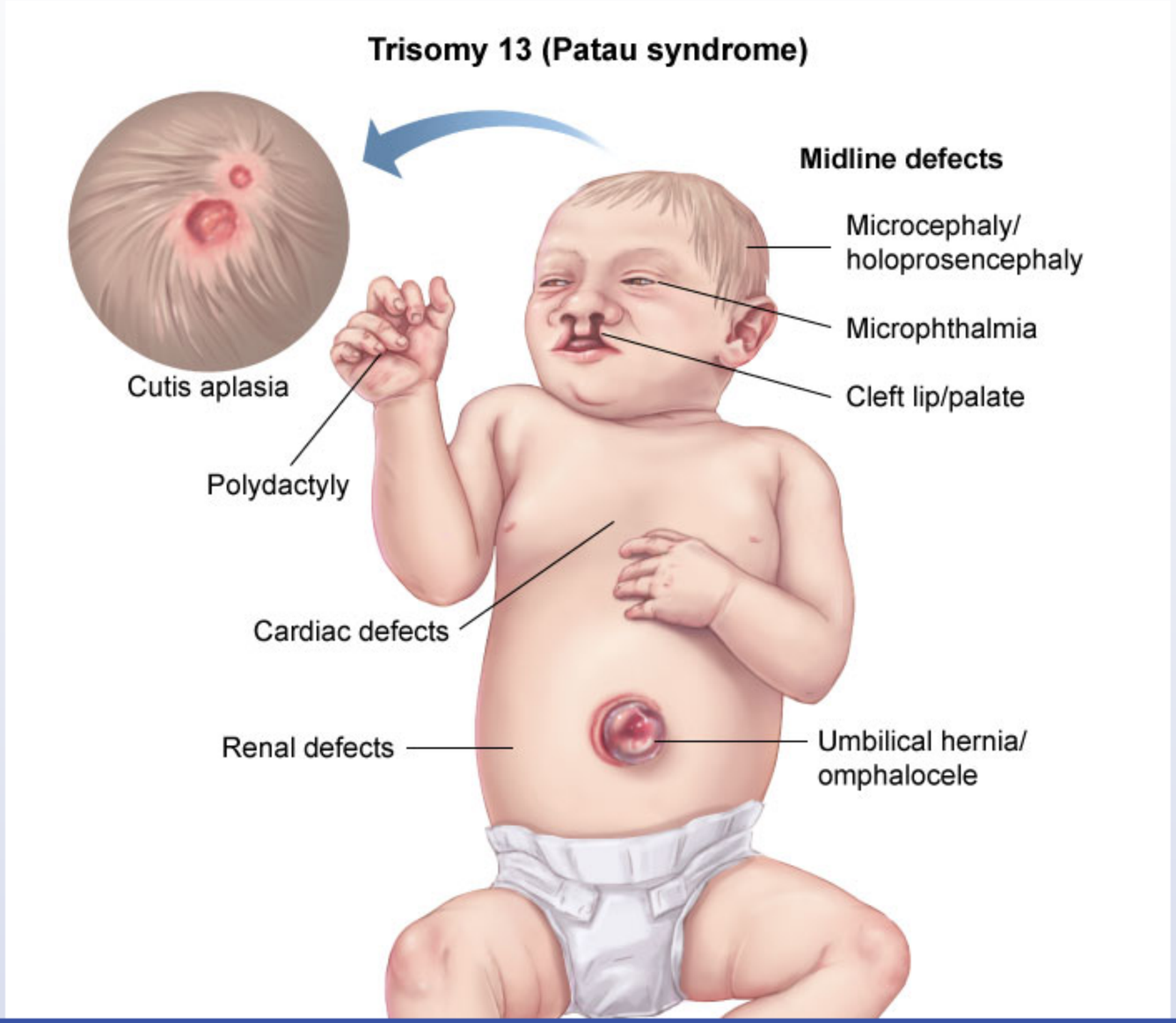

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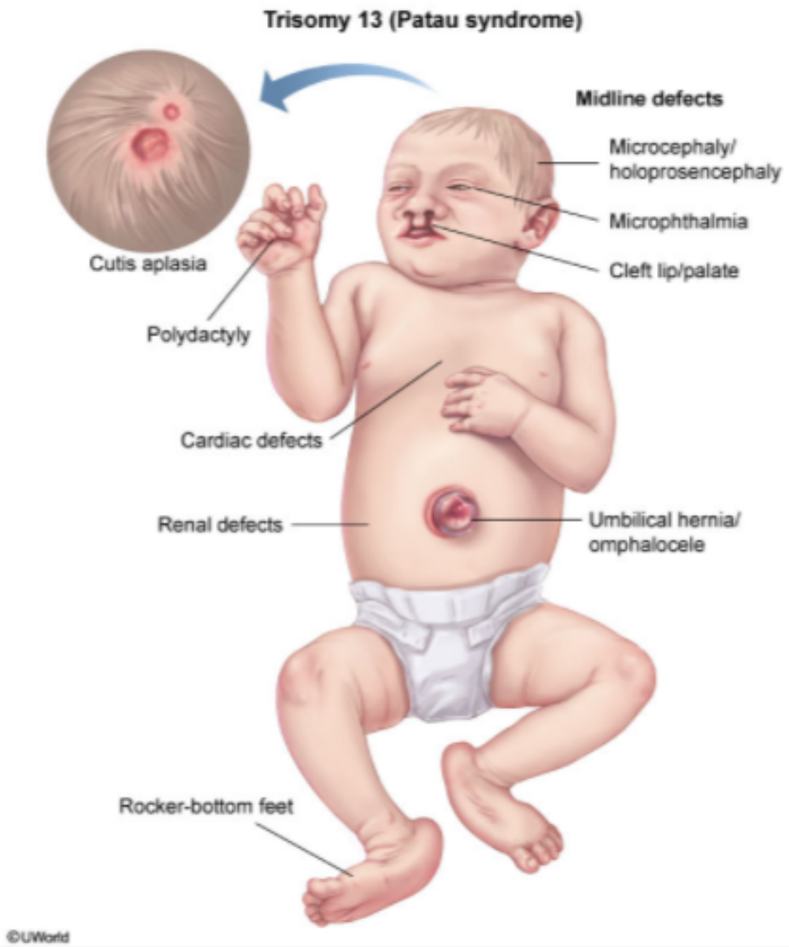

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Patau syndrome, or **trisomy 13**, is a severe genetic disorder with phenotypic features reflecting a defect in the fusion of the **prechordal mesoderm**, an integral embryological structure affecting growth of the midface, eyes, and forebrain. This results in catastrophic midline defects, including holoprosencephaly, microcephaly, **microphthalmia**, **cleft lip/palate**, and omphalocele. Abnormal brain development results in intellectual disability and seizures. Additional abnormalities include **polydactyly** and **cutis aplasia** (focal skin defect of the scalp). The majority of patients with Patau syndrome die in utero; only 5% survive beyond 6 months.

Cytogenetic studies usually demonstrate meiotic nondisjunction, which is the failure of chromosomal separation during meiosis, causing inheritance of a chromosome pair from 1 parent rather than a single chromatid. Maternal age ≥35 is an important risk factor for this abnormality of oocyte division. Nondisjunction results in a fetus with 3 complete copies of chromosome 13 (47, XX, +13).

(Choice A) Patients with Down syndrome (trisomy 21) typically have a flat facial profile, upslanting palpebral fissures, low-set small ears, redundant skin at the nape of the neck, single transverse palmar crease, and hypotonia. Increased rates of duodenal atresia and Hirschsprung disease are seen in these patients.

(Choice B) Clinical manifestations of Edwards syndrome (trisomy 18) include fetal growth retardation, hypertonia, micrognathia, and congenital heart defects. Additional features include clenched hands with overlapping fingers, Meckel's diverticulum, and malrotation.

(Choice C) Nicotine use during pregnancy increases the risk of prematurity and low birth weight. Related pregnancy complications include placenta previa and abruption.

(Choice D) Fetal exposure to maternal phenytoin has been associated with several congenital anomalies (eg, cardiac defects, cleft lip/palate, hypoplastic nails). It is not associated with cutis aplasia or omphalocele.

(Choice E) Congenital rubella syndrome typically occurs after a first trimester maternal rubella infection. Abnormalities classically include hearing loss, cataracts, and cardiac defects.

(Choice G) Williams syndrome is a genetic disorder classically associated with "elfin" facies, supravalvular aortic stenosis, and an extroverted personality.

Educational objective:
Patau syndrome (trisomy 13) usually occurs secondary to meiotic nondisjunction in mothers of advanced maternal age. Key physical findings

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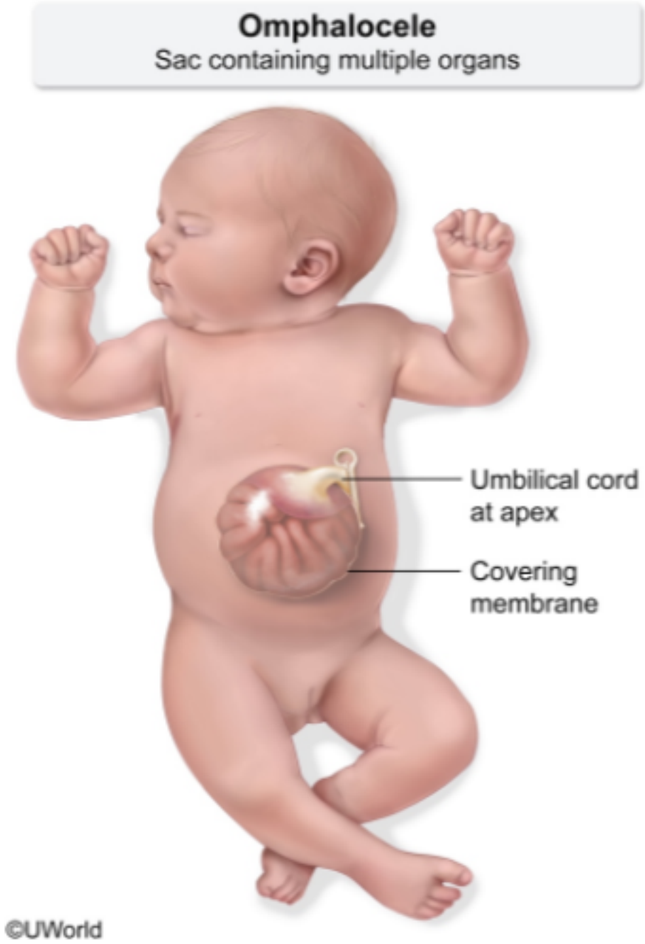

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Patau syndrome (trisomy 13) usually occurs secondary to meiotic nondisjunction in mothers of advanced maternal age. Key physical findings

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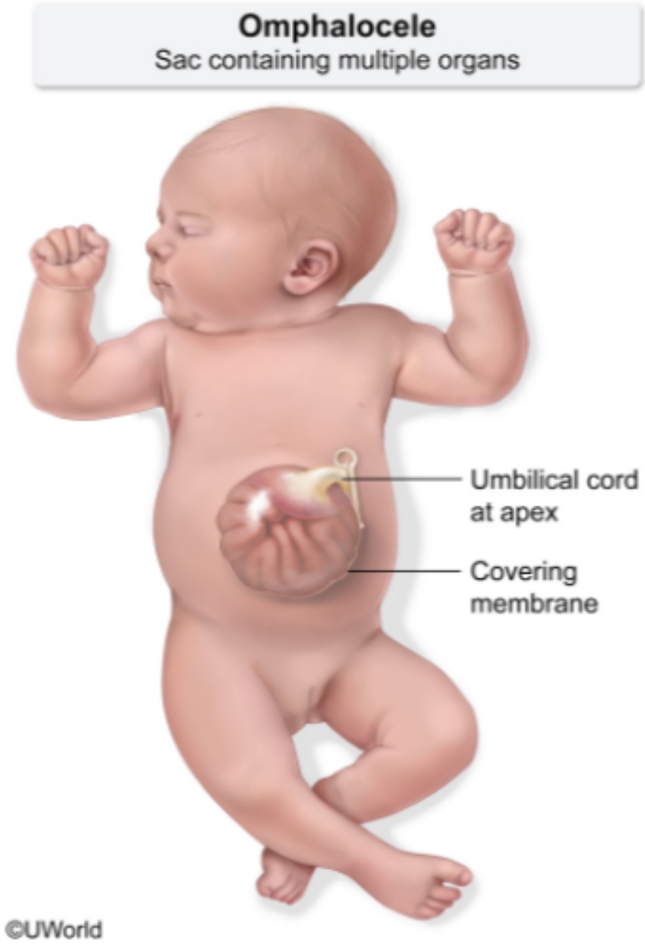

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Patau syndrome (trisomy 13) usually occurs secondary to meiotic nondisjunction in mothers of advanced maternal age. Key physical findings

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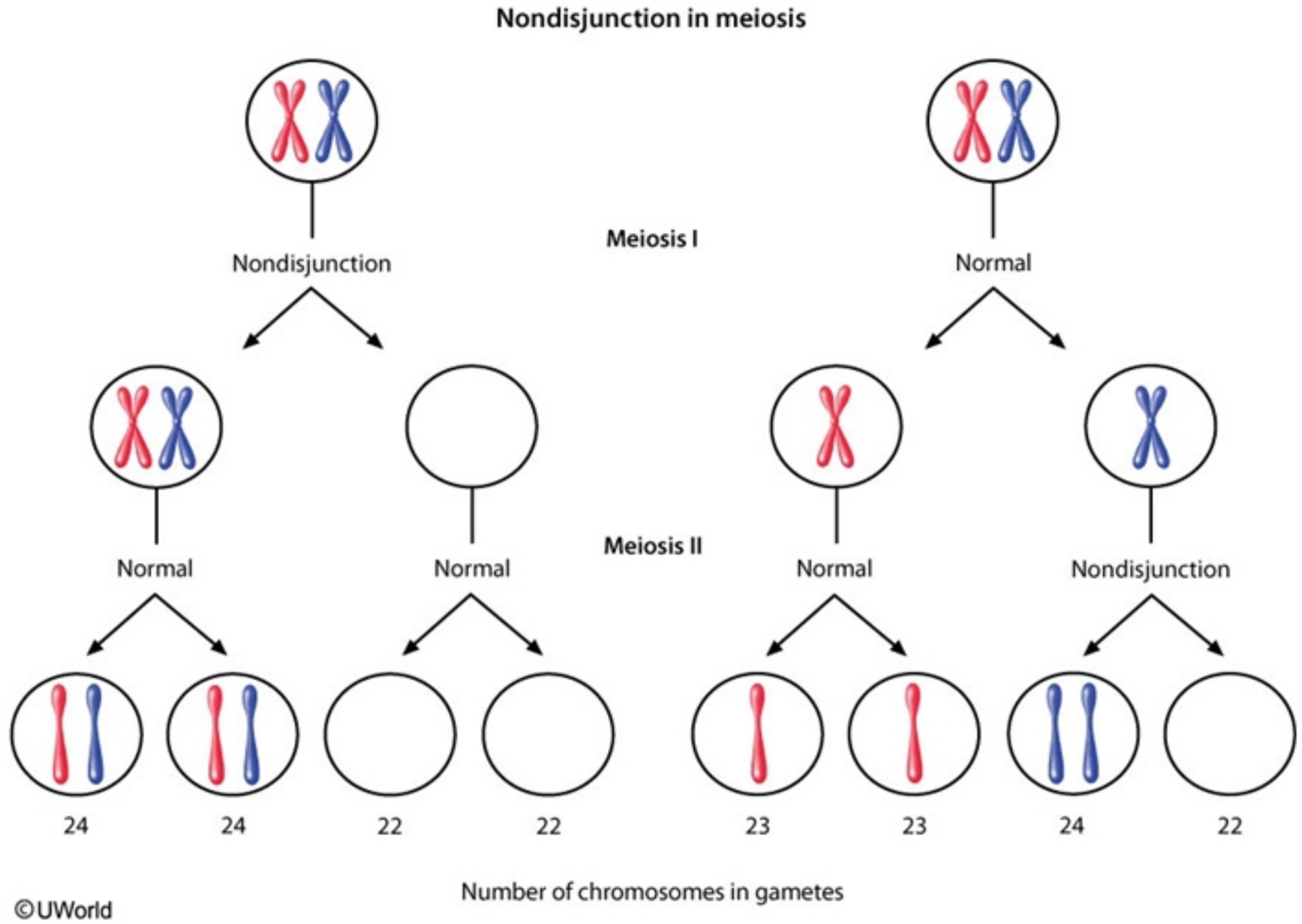

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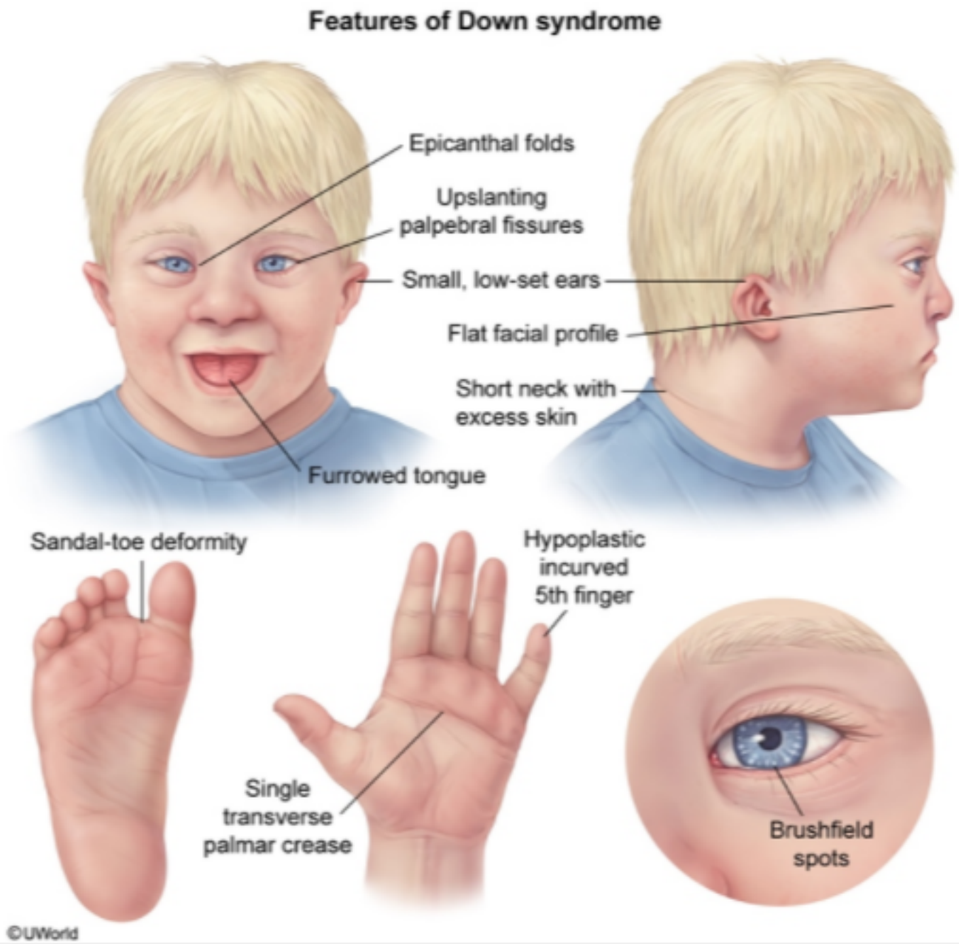

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Patau syndrome (trisomy 13) usually occurs secondary to meiotic nondisjunction in mothers of advanced maternal age. Key physical findings

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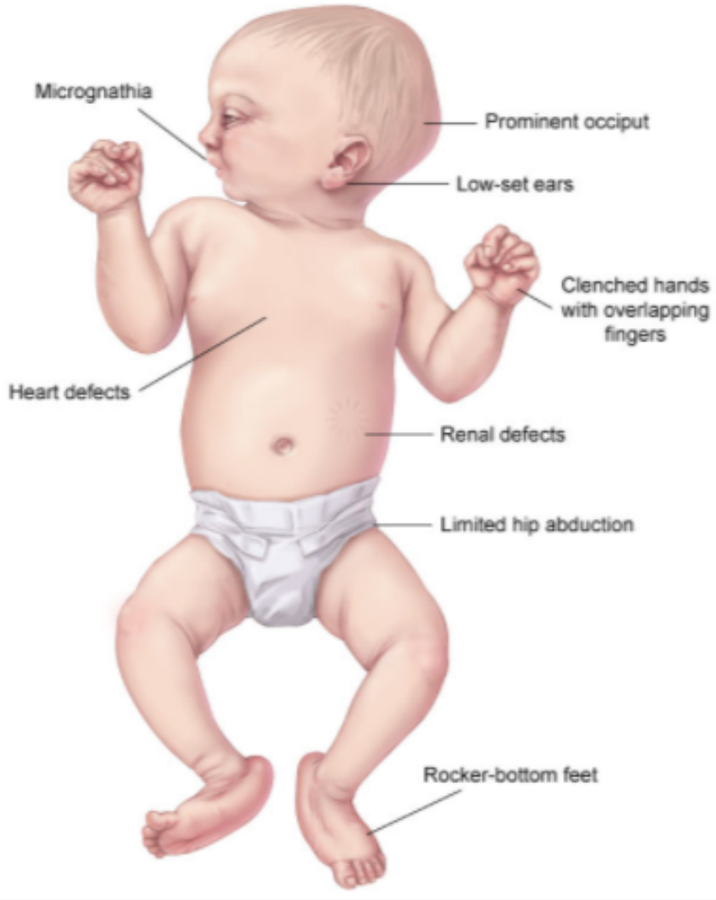
Trisomy 18 (Edwards syndrome)



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Patau syndrome (trisomy 13) usually occurs secondary to meiotic nondisjunction in mothers of advanced maternal age. Key physical findings

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A 15-year-old patient is referred to the physician by a teacher who is concerned about the patient's learning abilities and behavior. The patient's reading and writing skills are significantly impaired compared to other classmates, and the patient often misbehaves in class despite receiving numerous detentions. Neuropsychological assessment shows mild intellectual disability. Cytogenetic studies show a karyotype containing 47 chromosomes. Which of the following findings are most likely to be present on further evaluation?

A. Arachnodactyly, scoliosis, aortic root dilation

B. Macroorchidism, large jaw and ears

C. Short stature, broad chest, amenorrhea

D. Short stature, hypotonia, obesity

E. Tall stature, gynecomastia, azoospermia

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A. Arachnodactyly, scoliosis, aortic root dilation (2%)

B. Macroorchidism, large jaw and ears (15%)

C. Short stature, broad chest, amenorrhea (4%)

D. Short stature, hypotonia, obesity (6%)

✓ E. Tall stature, gynecomastia, azoospermia (70%)

Omitted
Correct answer
E

70%
Answered correctly

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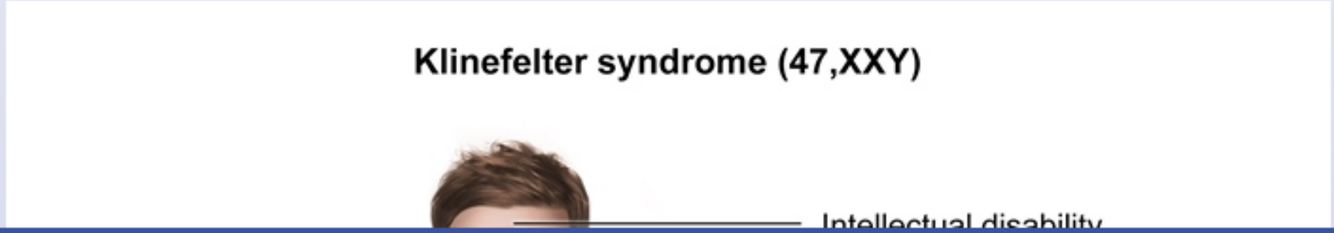
Explanation



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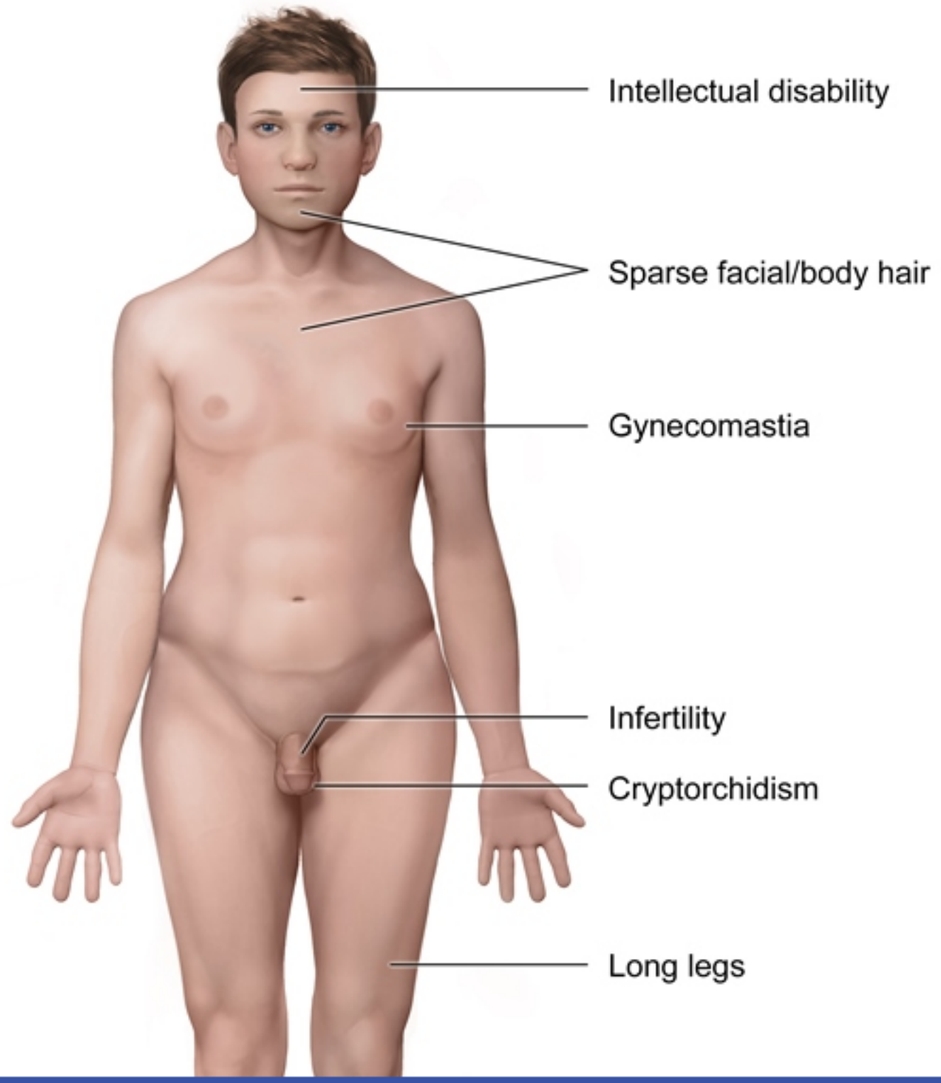
Klinefelter syndrome (47,XXY)



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Klinefelter syndrome is most commonly caused by a meiotic nondisjunction event during parental gametogenesis that results in a **47,XXY** karyotype. Variants include 46,XY/47,XXY mosaicism and 48,XXXY. In general, patients with higher numbers of X chromosomes are more likely to have more severe manifestations. The disorder is usually not diagnosed until puberty when the characteristic physical signs begin to develop. The major features are as follows:

1. Klinefelter syndrome causes **primary testicular failure** due to hyalinization and fibrosis of the seminiferous tubules. This results in small, firm testes and azoospermia (infertility). Leydig cell dysfunction also occurs and leads to testosterone deficiency. Gonadotropin (FSH, LH) levels are increased secondary to gonadal failure.
2. Testosterone deficiency results in development of a **eunuchoid body habitus**. Patients have tall stature and gynecomastia. Facial and body hair is sparse or absent and muscle mass is decreased.
3. Mild **intellectual disability** is seen in some patients, although the majority have normal intelligence. Psychosocial abnormalities (eg, lack of insight, poor judgment) are also common.

(Choice A) Arachnodactyly, scoliosis, and aortic root dilation are signs of Marfan syndrome, which occurs due to an inherited defect of the extracellular matrix protein fibrillin.

(Choice B) Macroorchidism, large jaw, and intellectual disability are seen in patients with fragile X syndrome, an X-linked disorder caused by mutations in the fragile X mental retardation 1 gene.

(Choice C) In females, loss of an X chromosome (45,XO karyotype) results in Turner syndrome, which presents with short stature, broad chest, and primary amenorrhea.

(Choice D) Prader-Willi syndrome is characterized by short stature, hypotonia, intellectual disability, and obesity. The most common cause is a microdeletion affecting the paternal chromosome 15q11-13 critical region.

Educational objective:
47,XXY is the most common genotype causing Klinefelter syndrome. Patients present with tall stature; small, firm testes; azoospermia; and gynecomastia. Mild intellectual disability is seen in some patients, and the severity generally increases with each additional X chromosome.

References

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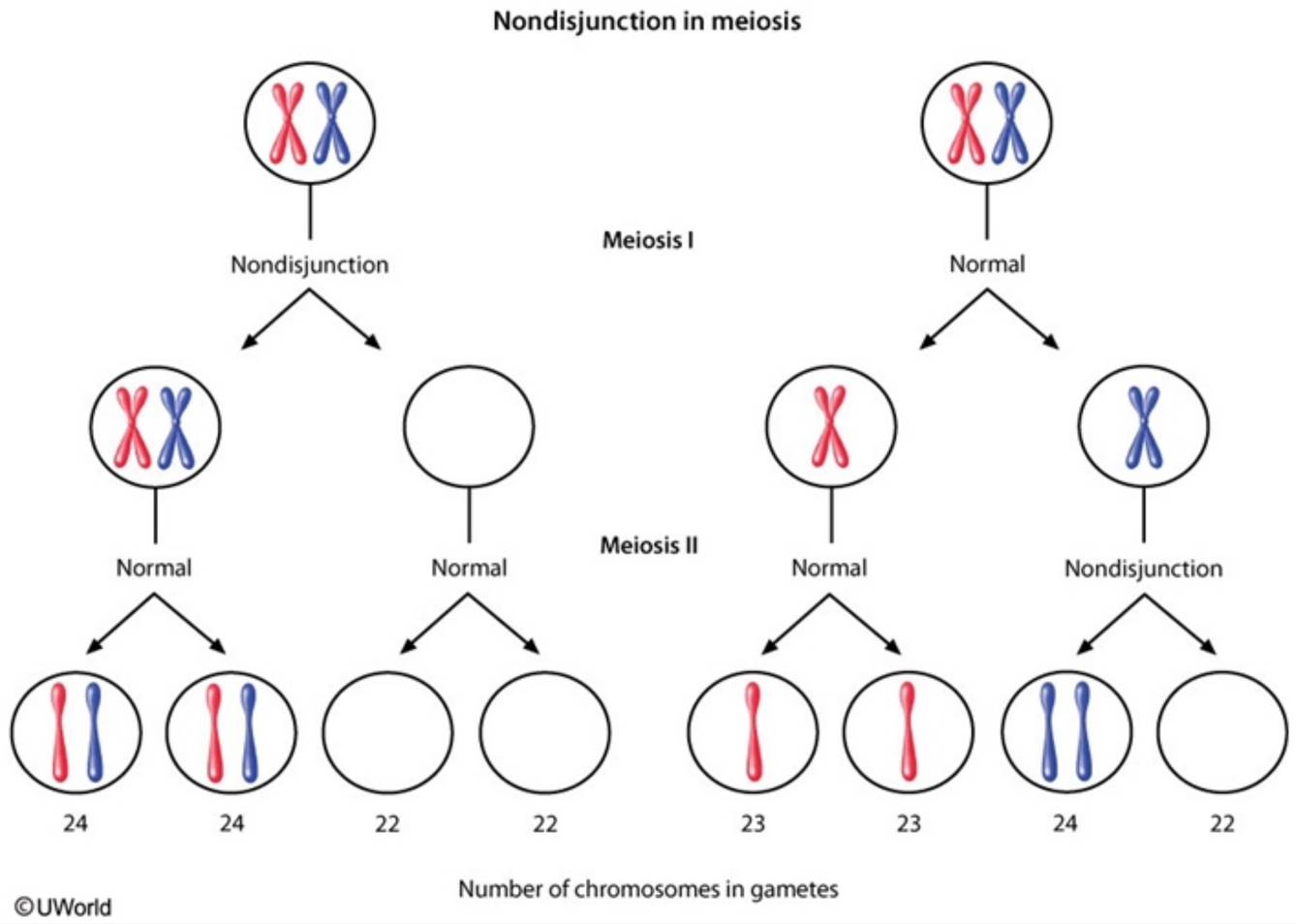

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References

firm testes and azoospermia (infertility). Leydig cell dysfunction also occurs and leads to testosterone deficiency. Gonadotropin (FSH, LH) levels are increased secondary to gonadal failure.

2. Testosterone deficiency results in development of a **eunuchoid body habitus**. Patients have tall stature and gynecomastia. Facial and body hair is sparse or absent and muscle mass is decreased.
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Educational objective:
47,XXY is the most common genotype causing Klinefelter syndrome. Patients present with tall stature; small, firm testes; azoospermia; and gynecomastia. Mild intellectual disability is seen in some patients, and the severity generally increases with each additional X chromosome.

References

- The cognitive phenotype in Klinefelter syndrome: a review of the literature including genetic and hormonal factors.

Genetics	Male Reproductive System	Klinefelter syndrome
Subject	System	Topic

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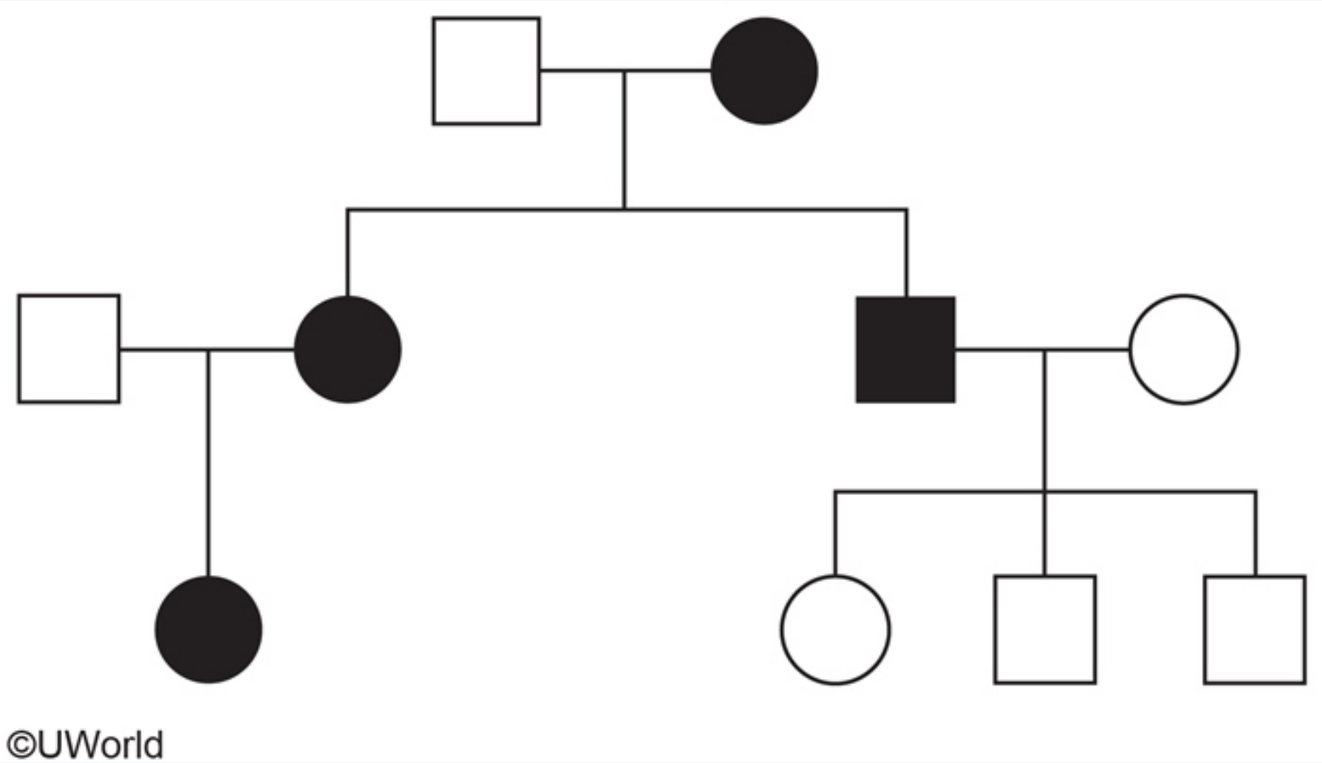
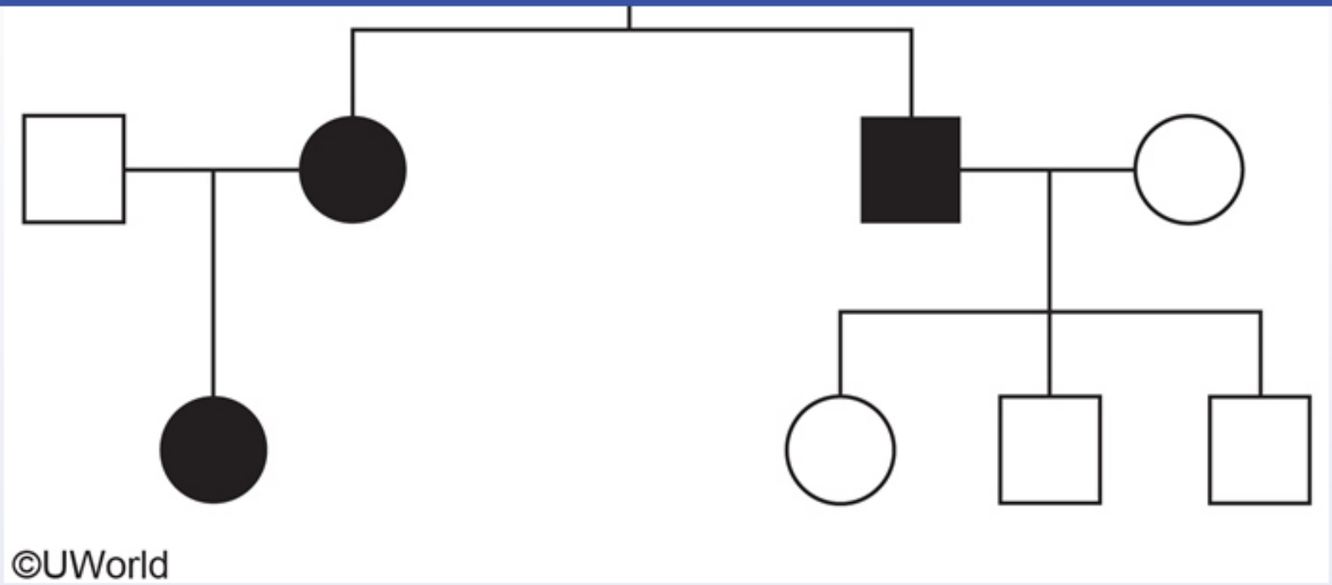
A 26-year-old woman is being evaluated for a possible inherited disorder. She has a 6-year history of generalized tonic-clonic seizures, and a year ago, she had partial loss of vision due to an occipital infarction. Her mother has chronic intermittent muscle weakness and lactic acidosis, and her maternal uncle has hemiplegia. Skeletal muscle biopsy of the patient shows ragged-appearing muscle fibers. After further evaluation, all the affected family members are found to suffer from the same inherited disease. Pedigree analysis is shown in the image below.



Which of the following is the most likely explanation for the variability of clinical manifestations in the affected family members?

A. Anticipation



Which of the following is the most likely explanation for the variability of clinical manifestations in the affected family members?

- A. Anticipation
- B. Heteroplasmy
- C. Incomplete penetrance
- D. Mosaicism
- E. Uniparental disomy

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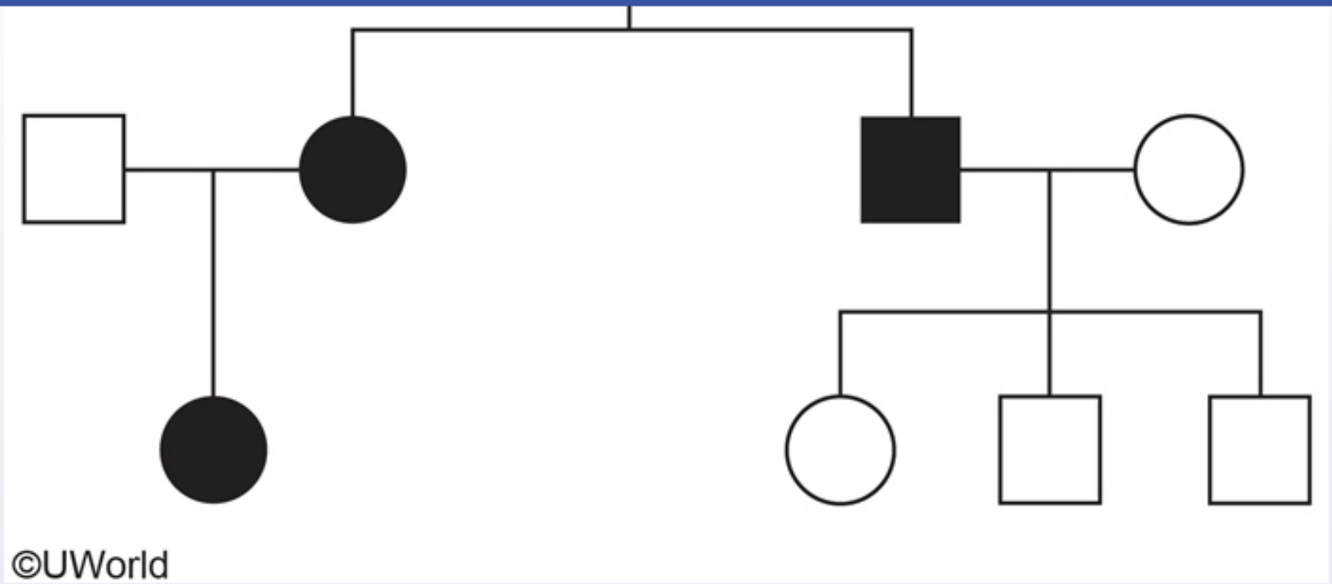

Which of the following is the most likely explanation for the variability of clinical manifestations in the affected family members?

- A. Anticipation (2%)
- ✓ B. Heteroplasmy (69%)
- C. Incomplete penetrance (12%)
- D. Mosaicism (9%)
- E. Uniparental disomy (5%)

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Correct answer

69%
Answered correctly

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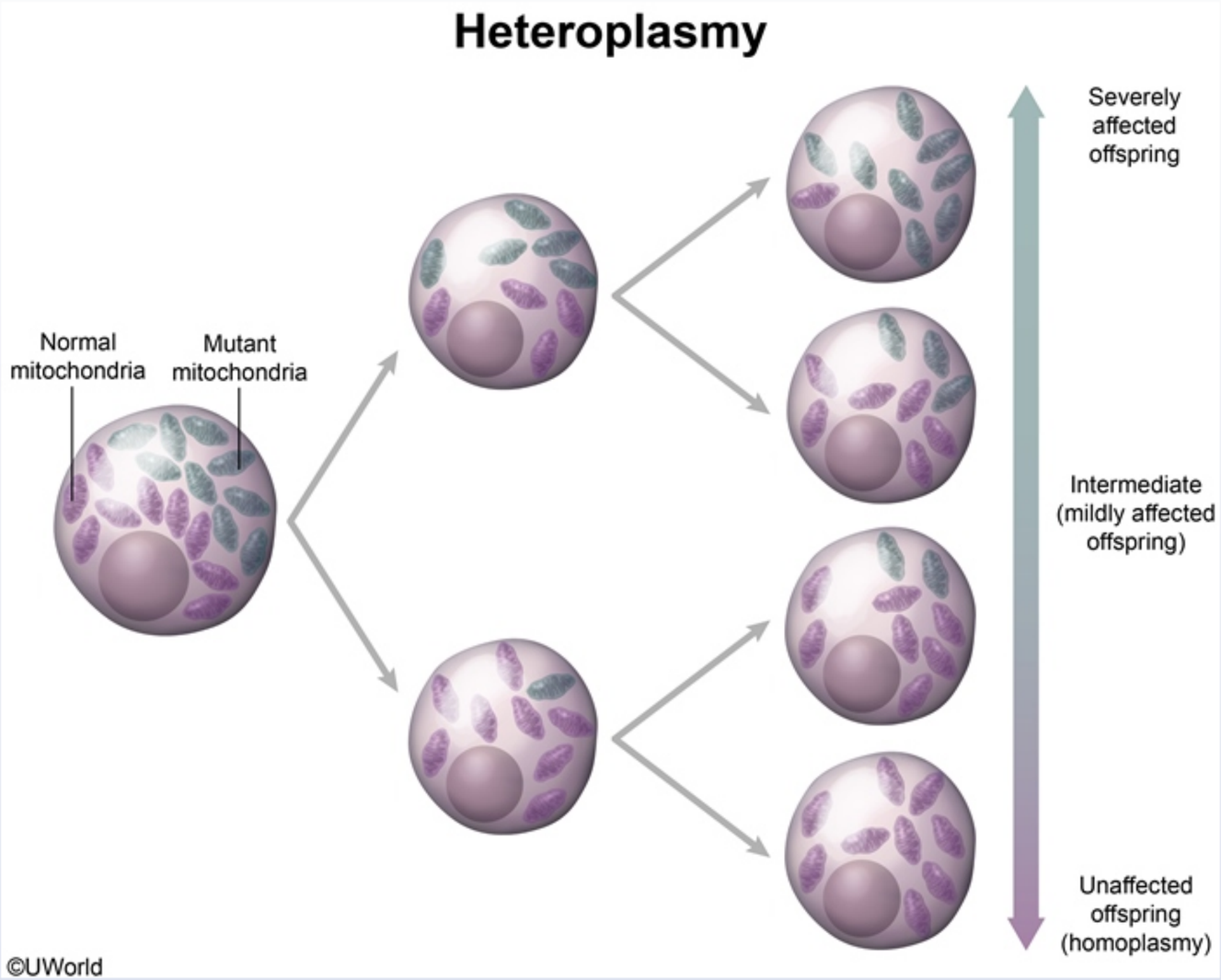

The neuromuscular lesions, ragged skeletal muscle fibers, and lactic acidosis in these family members suggest **mitochondrial encephalomyopathy**. Mitochondrial disorders follow a **maternal inheritance pattern** because an embryo's mitochondria are inherited from the

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The neuromuscular lesions, ragged skeletal muscle fibers, and lactic acidosis in these family members suggest **mitochondrial encephalomyopathy**. Mitochondrial disorders follow a **maternal inheritance pattern** because an embryo's mitochondria are inherited from the ovum only.

Mitochondria are responsible for ATP production via oxidative phosphorylation, which is why mitochondrial defects tend to cause lactic acidosis and primarily affect tissues with the highest metabolic rates (eg, neural tissue, muscular tissue). Although many mitochondrial proteins are coded for in the nuclear genome, mitochondria also contain their own genome, which is vulnerable to mutations. Each cell has hundreds of mitochondria, and defects in their genome may occur in any number of the mitochondria within the cell. **Heteroplasmy** describes the condition of having **different mitochondrial genomes** within a single cell. The severity of mitochondrial diseases is often directly related to the proportion of abnormal to normal mitochondria within a patient's cells.

(Choice A) Anticipation refers to increased severity or earlier onset of an inherited disease in successive generations. It is commonly seen in autosomal and X-linked trinucleotide repeat disorders due to trinucleotide amplification during gametogenesis.

(Choice C) Penetrance is the probability that a person with a given genotype will express its associated phenotype. If all individuals with a given gene express its phenotype, that gene is said to have complete penetrance.

(Choice D) Mosaicism refers to the presence of 2 or more cell lines, each with a unique nuclear genome, within the same individual. While patients with combined somatic and germline mosaicism can demonstrate disease traits and also pass the disease on to their offspring, mosaicism would not explain the pattern of female-only transmission.

(Choice E) Uniparental disomy occurs when both members of a chromosomal pair are inherited from one parent, which can cause problems due to genomic imprinting. For instance, although most often due to chromosomal deletions, uniparental disomy can also cause Prader-Willi and Angelman syndromes due to loss of expression of maternal/paternal imprinted components of a critical region of chromosome 15.

Educational objective:
The presence of lactic acidosis and ragged skeletal muscle fibers histologically suggests a mitochondrial myopathy. Variable clinical expressions in affected family members can occur due to heteroplasmy, which is the coexistence of distinct versions of mitochondrial genomes in an individual cell.

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References

- Epigenetics, epidemiology and mitochondrial DNA diseases.
- Mitochondrial disease in childhood: mtDNA encoded.

Genetics	Rheumatology/Orthopedics & Sports	Mitochondrial disorders
Subject	System	Topic

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A 43-year-old man is evaluated for progressive neuropsychiatric symptoms. A year ago, he began feeling depressed and having hallucinations. Five months later, he developed intermittent paresthesias and progressively worsening choreiform movements, myoclonus, and ataxia. These symptoms have not improved despite multiple hospitalizations; an extensive workup has been unrevealing. The patient is a slaughterhouse worker with extensive exposure to bovine offal. As part of the evaluation for prion disease, a tissue sample digested with protease is processed via gel electrophoresis and transferred to filter paper. Antibodies to a specific prion protein are added to the filter. Next, a marked protein that combines with the antibody-protein complex is used to determine whether the test is positive. Which of the following best describes this test?

A. Microarray
B. Northern blot
C. Southern blot
D. Southwestern blot
E. Western blot

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A. Microarray (5%)

B. Northern blot (2%)

C. Southern blot (3%)

D. Southwestern blot (5%)

✓ E. Western blot (83%)

Omitted
Correct answer
E

83%
Answered correctly

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Explanation

Western blotting is used to detect a target polypeptide or **protein** from within a mixed sample. Potential target proteins are separated by gel **electrophoresis**. The separated proteins are then transferred to a nitrocellulose membrane and probed with a primary **antibody** specific for the protein of interest. The membrane is then washed and treated with a (secondary) **marked antibody** that binds to the primary antibody and can be detected (eg, by colorimetry).

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For example, a serum sample from a patient with suspected HIV infection can be analyzed via Western blot to detect antibodies directed against specific viral proteins. Following separation of viral proteins by gel electrophoresis and protein transfer to a nitrocellulose membrane, the membrane is treated with the patient's serum. Patients who are HIV positive are likely to have antibodies that react with viral p24, gp41, and gp120/160. If 2 of these 3 bands are positive, the test is considered positive.

Western blotting is similar to the enzyme-linked immunosorbent assay (ELISA) technique; however, in ELISA the patient's serum is tested directly, whereas in Western blotting the proteins are first separated by electrophoresis.

(Choice B) Northern blots analyze **mRNA**. A sample containing a large number of mRNA molecules is separated via gel electrophoresis. Separated bands are then transferred to a membrane and hybridized with a probe containing a nucleotide sequence complementary to the mRNA of interest.

(Choice C) Southern blotting is used to analyze **DNA** sequences. DNA that is fragmented using restriction endonucleases is separated by gel electrophoresis and transferred to a nitrocellulose membrane. A radiolabeled DNA probe containing a sequence complementary to an area of interest is then used for hybridization. Restriction site mutations can be detected by Southern blotting because they alter DNA fragment lengths, thereby altering electrophoresis migration patterns.

Microarray analysis is similar to Southern and Northern blotting but involves hybridization of a large number of probes at once **(Choice A).** The genomic DNA or cDNA being analyzed is labeled with a fluorescent tag and placed on a gene chip containing complementary sequences for a large number of genes. The degree of fluorescence corresponds to the mRNA expressed in the particular sample.

(Choice D) Southwestern blotting is a technique that analyzes DNA-binding proteins using principles of the Southern and Western blot techniques. DNA-binding proteins are recognized by their ability to bind specific oligonucleotide probes.

Educational objective:

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Educational objective:
Western blotting is used to identify proteins, Northern blotting identifies specific RNA sequences, and Southern blotting identifies specific DNA sequences in an unknown sample.

Genetics	Hematology & Oncology	Prion disease
Subject	System	Topic

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membrane is treated with
gp120/160. If 2 of these 3

Western blotting is similar ctly,
whereas in Western blottir

(Choice B) Northern blo
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of interest.

(Choice C) Southern blo el
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thereby altering electroph

Microarray analysis is sim e
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(Choice D) Southwestern
techniques. DNA-binding

Educational objective:
Western blotting is used to
sequences in an unknown

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Genetics	Hematology & Oncology	Prion disease
Subject	System	Topic

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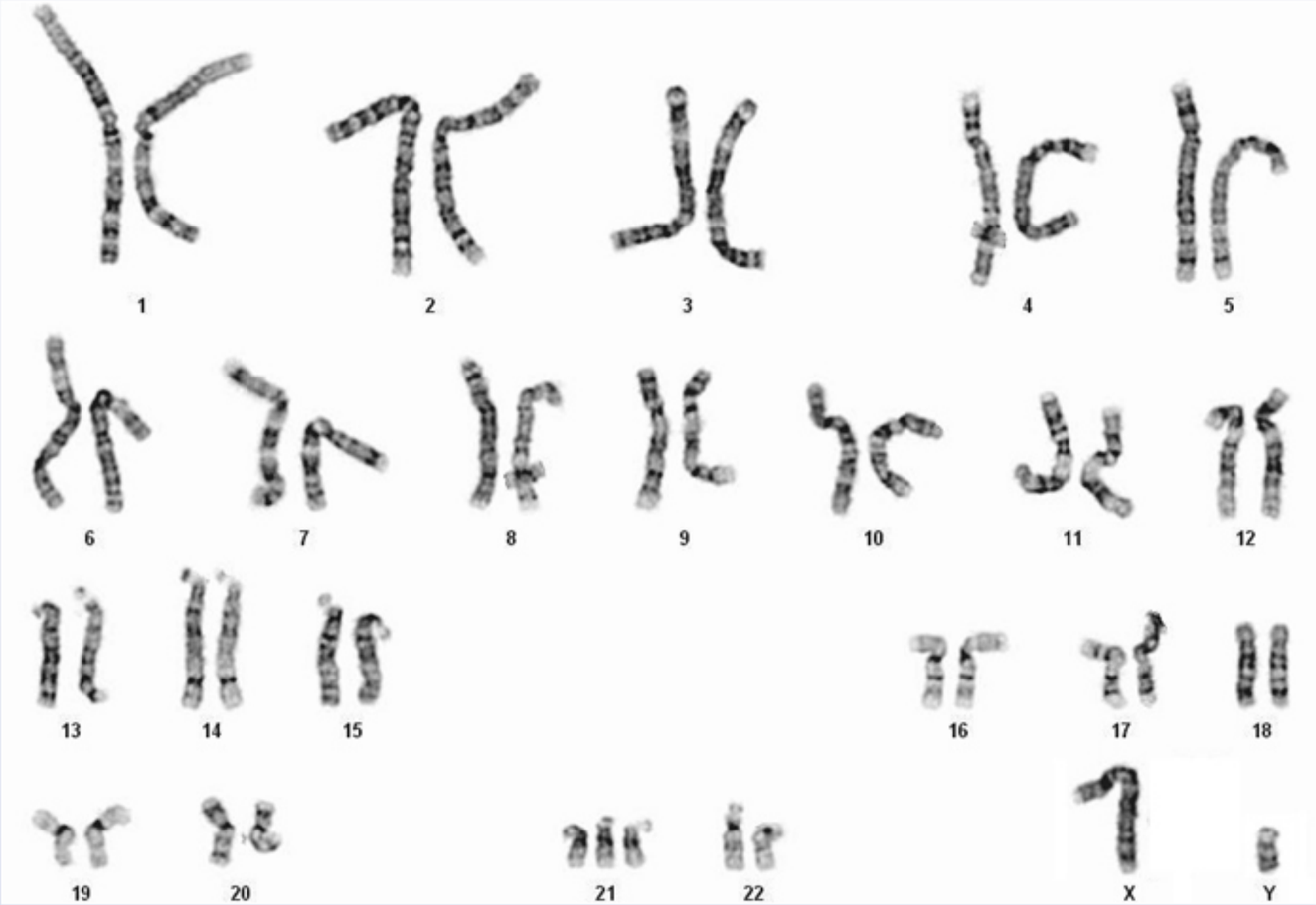
A 35-year-old woman and her husband have been trying to conceive for more than a year and are being followed by an infertility specialist. The woman is found to have significant scarring and fibrosis involving her fallopian tubes secondary to pelvic inflammatory disease that she had at a young age. After a long struggle, the woman finally becomes pregnant. She gives birth to a boy who is evaluated by a pediatrician and found to have a flat nasal bridge, small mouth, and low-set ears. The pediatrician orders a karyotype analysis on the infant, which is shown below.



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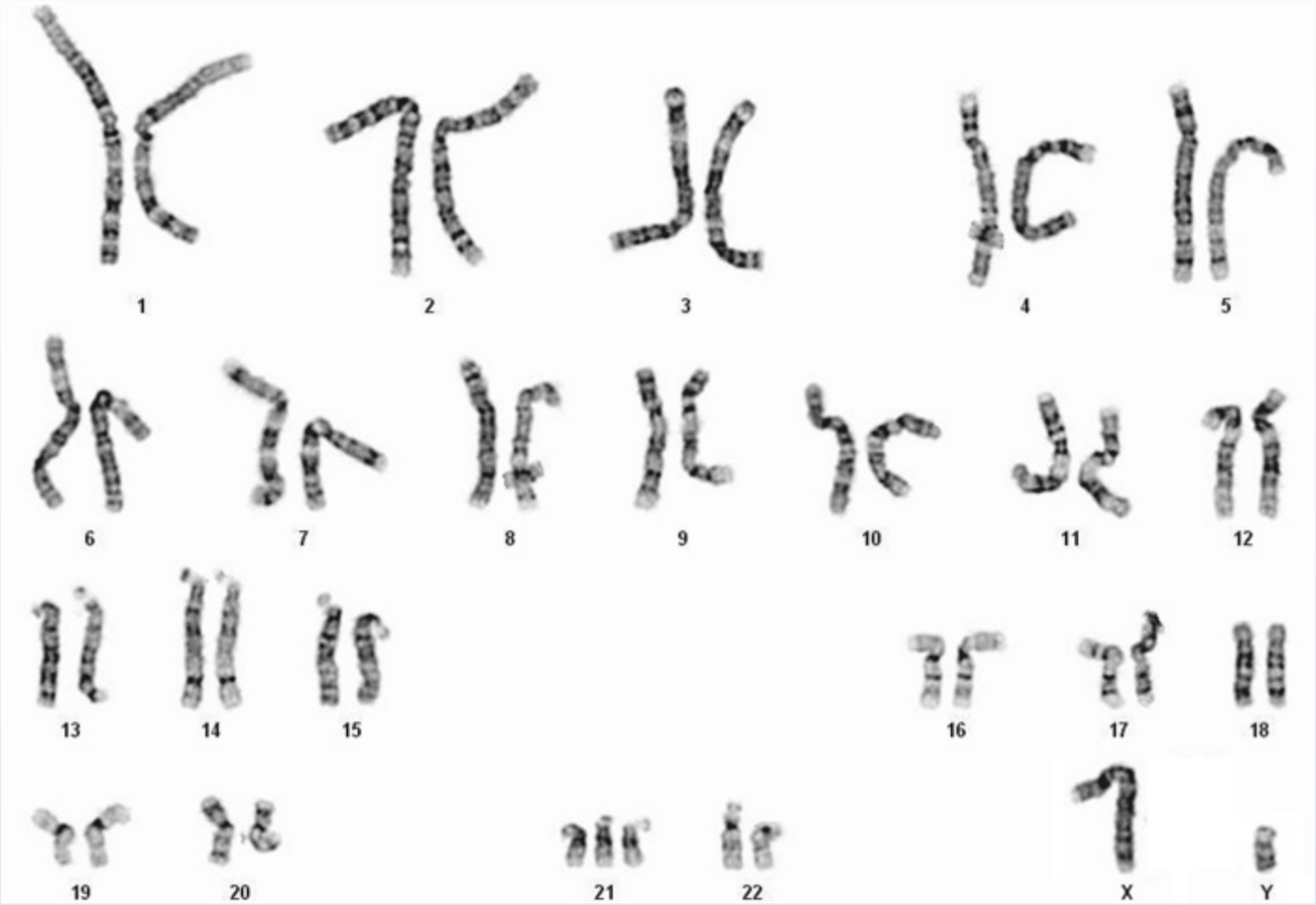

The infant is most likely to be diagnosed with which of the following conditions?

A. Acute lymphoblastic leukemia

B. Chronic myelogenous leukemia

C. Immotile cilia

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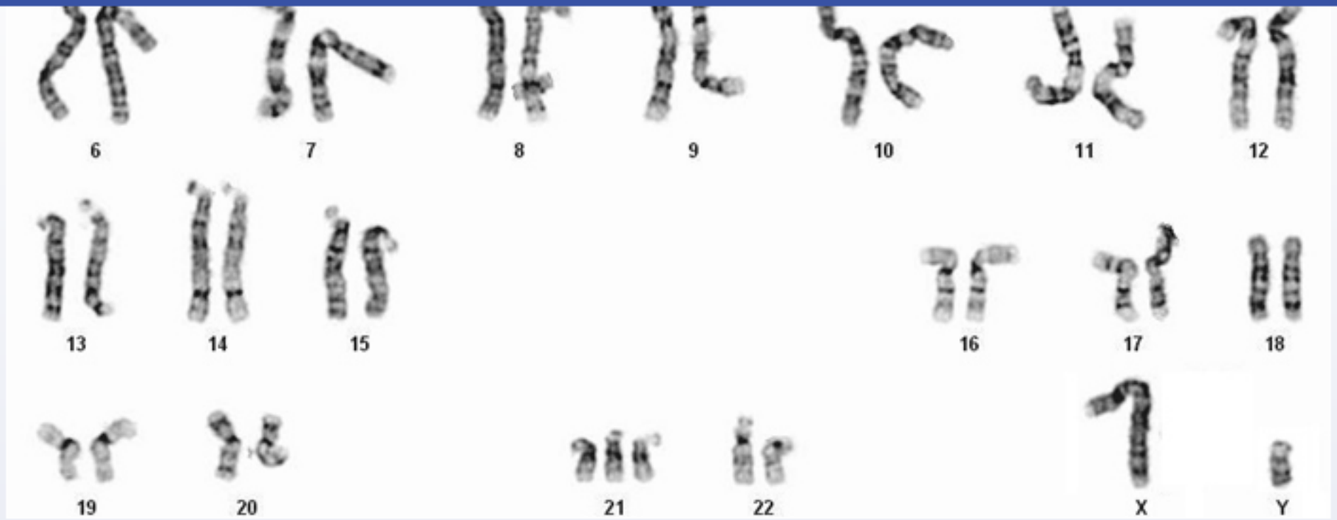

The infant is most likely to be diagnosed with which of the following conditions?

- A. Acute lymphoblastic leukemia
- B. Chronic myelogenous leukemia
- C. Immotile cilia
- D. Macroorchidism
- E. Red blood cell sickling
- F. Rickets

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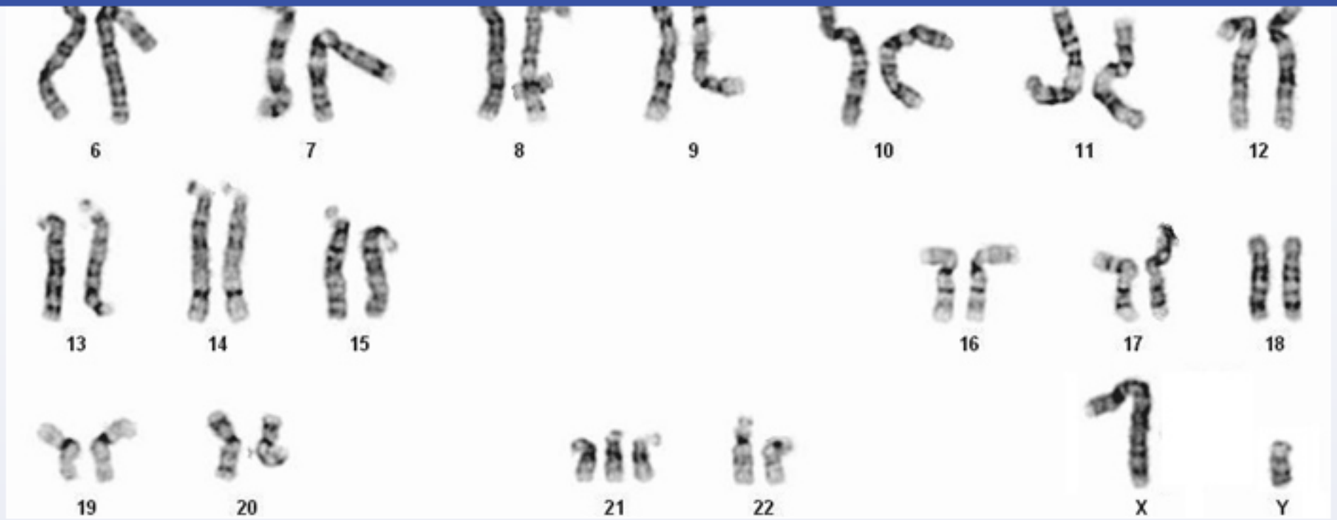

The infant is most likely to be diagnosed with which of the following conditions?

- ✓ A. Acute lymphoblastic leukemia (85%)
- B. Chronic myelogenous leukemia (8%)
- C. Immotile cilia (1%)
- D. Macroorchidism (3%)
- E. Red blood cell sickling (0%)
- F. Rickets (0%)

Omitted
Correct answer

85%
Answered correctly

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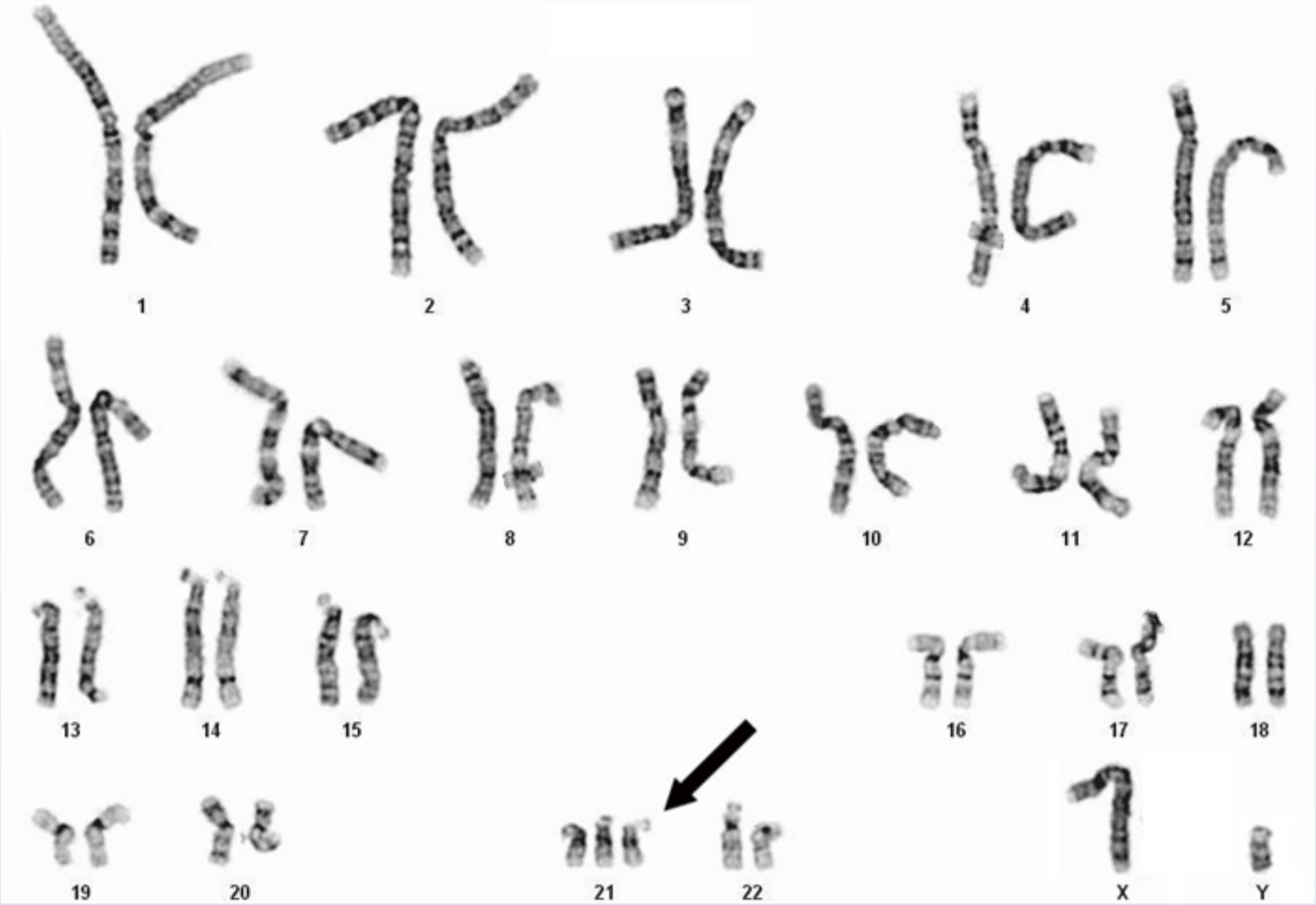

This karyotype shows **trisomy 21** (47, XY, +21), which is diagnostic for **Down syndrome**, the most common genetic cause of congenital **intellectual disability**. In most cases, Down syndrome results from meiotic nondisjunction in the ovum; the parents themselves are usually genetically normal. **Advanced maternal age** is a risk factor for having a child with Down syndrome.

Individuals with Down syndrome are at an increased risk of developmental abnormalities (eg, cardiac septal defects, duodenal atresia) and health complications (eg, early-onset Alzheimer disease, ophthalmologic disorders). They also have **increased risk** of hematologic malignancies such

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(Choice B) Chronic myelogenous leukemia is commonly associated with the Philadelphia chromosome (reciprocal translocation between the long arms of chromosomes 9 and 22). This translocation fuses the BCR gene on chromosome 22 to the ABL gene on chromosome 9, resulting in formation of the oncogenic BCR-ABL fusion gene on the shortened chromosome 22. Karyotype analysis shows elongation of chromosome 9 and shortening of chromosome 22.

(Choice C) Immotile cilia are found in Kartagener syndrome, a condition caused in most cases by an autosomal recessive mutation in the gene coding for the microtubule-associated protein dynein. Patients can have infertility, recurrent sinusitis, and bronchiectasis. Situs inversus may also be present.

(Choice D) Macroorchidism (ie, large testes) typically develops in pubertal boys with fragile X syndrome, the second most common genetic cause (and the most common inherited cause) of intellectual disability in males. On karyotype analysis, this X-linked disorder shows a discontinuity of staining on the long arm of the X chromosome.

(Choice E) Red blood cell sickling occurs in sickle cell anemia. The sickle cell mutation is localized to individual β-globin genes on chromosome 11 and does not result from trisomy 21.

(Choice F) Rickets can be caused by autosomal dominant, autosomal recessive, and X-linked mutations that affect calcium and phosphate metabolism and bone mineralization.

Educational objective:
Trisomy 21 is detectable by cytogenetic karyotype analysis and is the most common genetic cause of congenital intellectual disability. Patients with Down syndrome are at increased risk of developing acute lymphoblastic leukemia and acute megakaryoblastic leukemia.

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Trisomy 21 is detectable by cytogenetic karyotype analysis and is the most common genetic cause of congenital intellectual disability. Patients with Down syndrome are at increased risk of developing acute lymphoblastic leukemia and acute megakaryoblastic leukemia.

References

- Malignancy in children with trisomy 21.
- Down syndrome and malignancies: a unique clinical relationship: a paper from the 2008 william beaumont hospital symposium on molecular

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A 3-year-old boy is brought to the office for follow-up on intellectual disability and speech delay. Review of his developmental screening questionnaire shows that the boy does not imitate his parents' activities, have a social smile, or show interest in other children. The patient has 8-10 words in his vocabulary and does not combine them into 2-word phrases. There is also concern that his verbal comprehension is poor, and a subsequent audiological evaluation was normal. The boy is up to date on all vaccinations and has no other significant medical history. Laboratory testing shows 226 CGG trinucleotide repeats in a gene located on the X chromosome. Which of the following is the most likely cause of this patient's clinical condition?

A. Exon deletion
B. Gene methylation
C. Impaired intron splicing
D. Imprinting
E. Mismatch repair defect

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- A. Exon deletion (8%)
- ✓ B. Gene methylation (45%)
- C. Impaired intron splicing (28%)
- D. Imprinting (9%)
- E. Mismatch repair defect (8%)

Omitted
Correct answer
B

45%
Answered correctly

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01/12/2020
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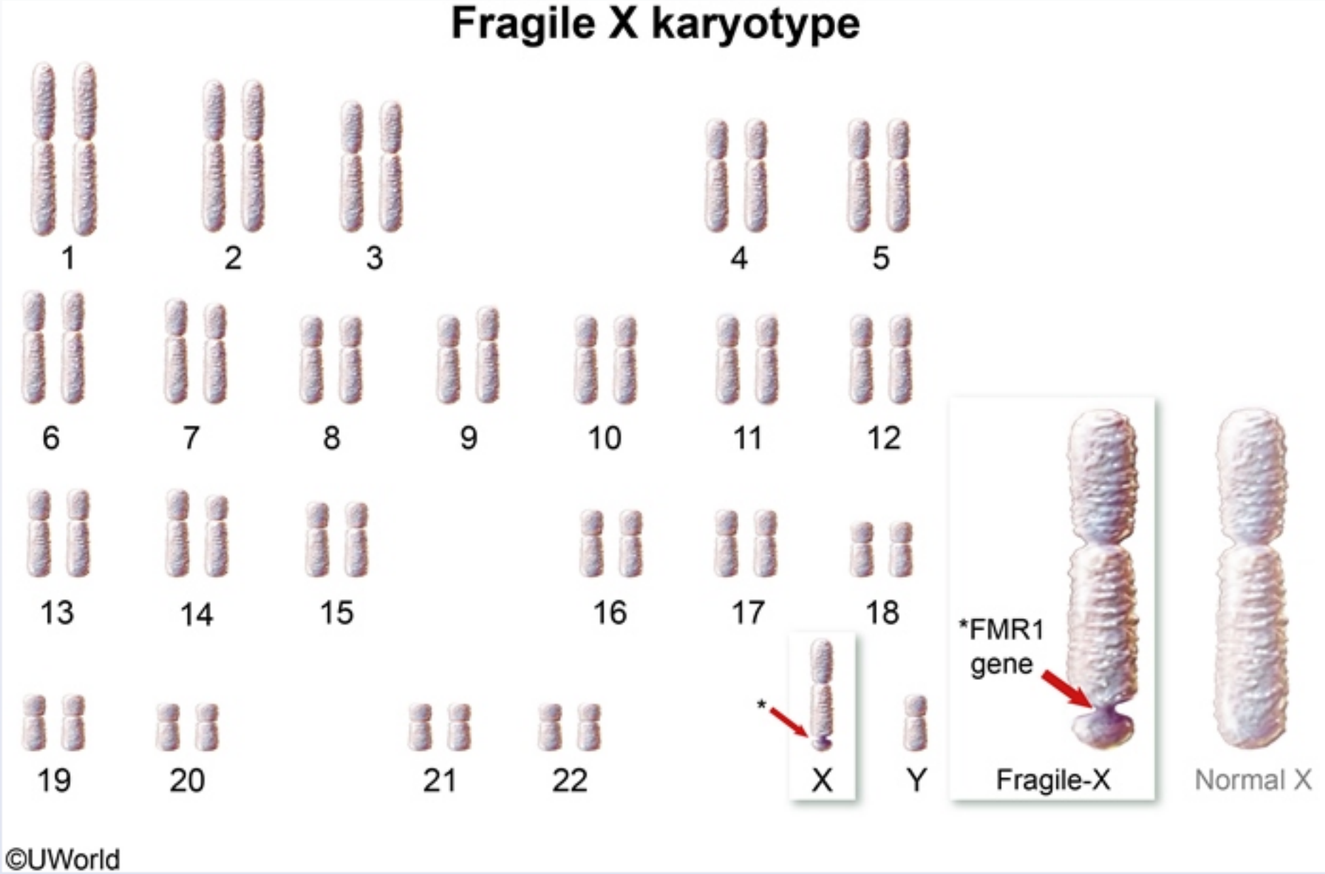
Explanation

Fragile X karyotype



This patient has **fragile X syndrome** (FXS), the most common inherited cause of **intellectual disability**. Physical findings include macroorchidism and dysmorphic facies (eg, long and narrow face, prominent forehead and chin). **Neuropsychiatric disorders** include developmental delay, attention deficit-hyperactivity disorder, and autism spectrum disorder (ASD). This patient's delayed language acquisition and poor social skills are suggestive of ASD.

FXS is caused by a mutation of the fragile X mental retardation 1 (*FMR1*) gene on the **long arm of the X chromosome**. *FMR1* normally has 5 to

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FXS is caused by a mutation of the fragile X mental retardation 1 (*FMR1*) gene on the **long arm of the X chromosome**. *FMR1* normally has 5 to 55 CGG trinucleotide repeats and can potentially expand during **meiosis in oocytes**. "Full mutation" is characterized by **>200 CGG trinucleotide repeats**, which causes ***FMR1* hypermethylation**. DNA methylation **inactivates** *FMR1*, preventing transcription and production of fragile X mental retardation protein, thereby impairing neural development. Southern blot analysis is used to measure the degree of methylation and determine the number of CGG repeats.

(Choices A and C) Exons ("**ex**pressed cod**ons**") are protein coding regions of DNA. Introns are removed during intranuclear mRNA processing and not expressed in the final mRNA sequence. Abnormalities involving mRNA splicing do not play a role in FXS pathogenesis.

(Choice D) Imprinting refers to gene expression from only one parental allele, rather than from both. A mutation in the preferentially expressed allele can result in Prader-Willi syndrome (PWS) or Angelman syndrome. PWS is caused by a paternally-inherited deletion of part of chromosome 15 while the maternal allele is not expressed. In contrast, Angelman syndrome is caused by a maternally-inherited deletion of the same portion of chromosome 15 while the paternal allele is not expressed.

(Choice E) Defects in DNA mismatch repair genes cause Lynch syndrome, a condition characterized by an increased risk of hereditary non-polyposis colorectal cancer and extraintestinal malignancies (eg, endometrial cancer).

Educational objective:
Fragile X syndrome is caused by an increased number of CGG trinucleotide repeats on the fragile X mental retardation 1 (*FMR1*) gene on the long arm of the X chromosome. This leads to hypermethylation and inactivation of *FMR1*.

References

- Fragile X syndrome
- FMR1: a gene with three faces

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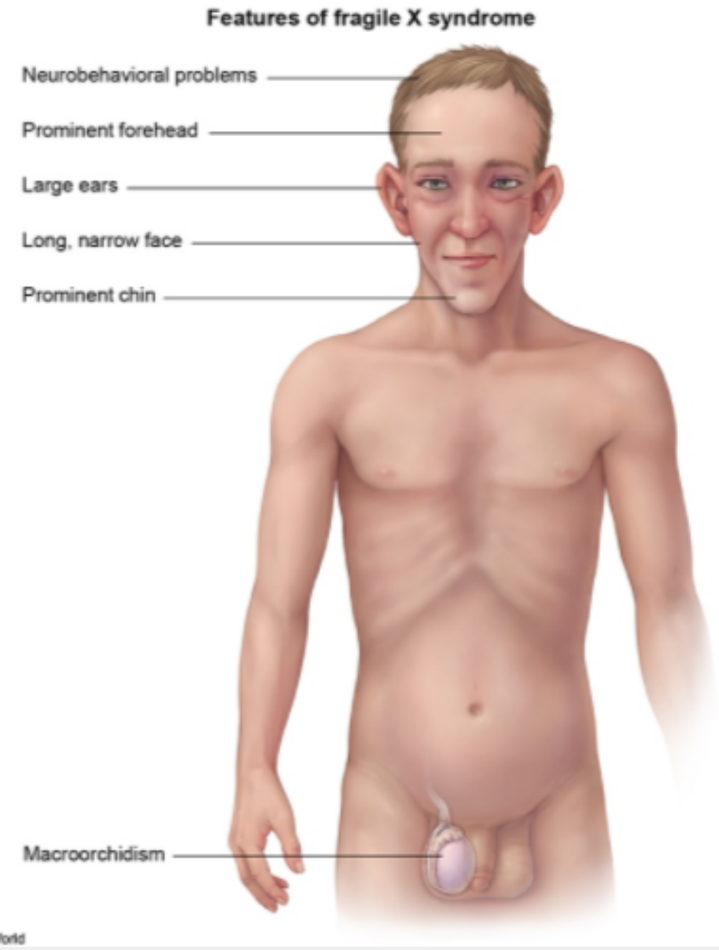

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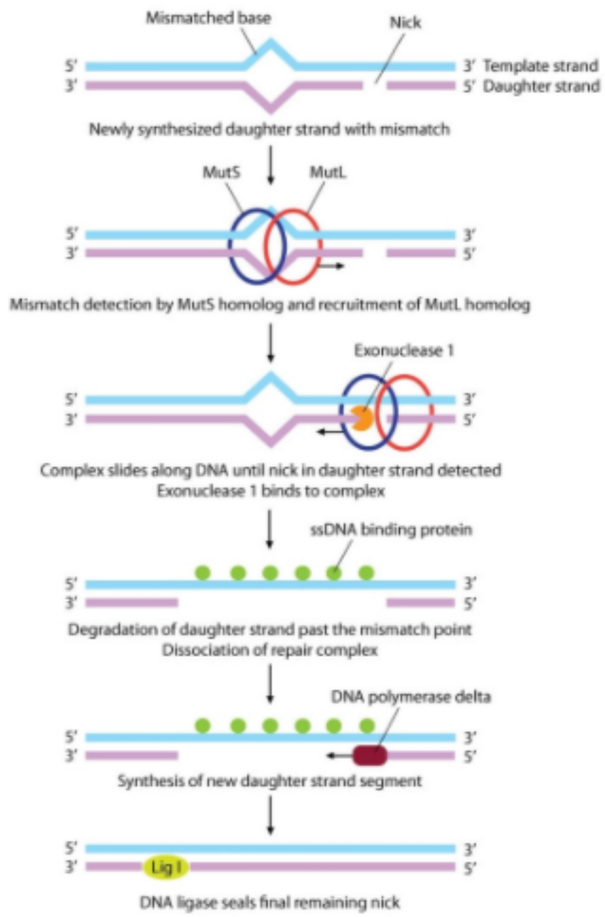

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A boy is admitted to the neonatal intensive care unit shortly after being born to a 28-year-old woman who had poor prenatal care. His temperature is 37.2 C (99 F), blood pressure is 70/30 mm Hg, pulse is 128/min, and respirations are 40/min. Pulse oximetry shows 85% on room air. Physical examination is significant for orbital hypertelorism, a submucous cleft palate, and bifid uvula. An echocardiogram reveals right ventricular hypertrophy, pulmonary stenosis with ventricular septal defect, and overriding aorta. The patient's diagnosis is eventually confirmed by fluorescence in situ hybridization. These findings are most consistent with which of the following mechanisms?

A. Abnormal ciliary motility
B. Chromosome microdeletion
C. Defect in fibrillin synthesis
D. Genomic imprinting
E. Mutation of tumor suppressor gene
F. Nucleotide repeat expansion

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- A. Abnormal ciliary motility (3%)
- ✓ B. Chromosome microdeletion (78%)
- C. Defect in fibrillin synthesis (4%)
- D. Genomic imprinting (5%)
- E. Mutation of tumor suppressor gene (1%)
- F. Nucleotide repeat expansion (5%)

Omitted
Correct answer
B

78%
Answered correctly

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Explanation

DiGeorge syndrome/velocardiofacial syndrome	
	• Chromosome 22q11.2 deletion

DiGeorge syndrome/velocardiofacial syndrome	
Pathogenesis	• Chromosome 22q11.2 deletion • Defective development of pharyngeal pouches
Clinical features	• **C**onotruncal **c**ardiac defects (tetralogy of Fallot, truncus arteriosus, interrupted aortic arch) • **A**bnormal facies • **T**hymic hypoplasia/aplasia (**T**-cell deficiency) • **C**raniofacial deformities (**c**left palate) • **H**ypocalcemia/**H**ypoparathyroidism

Chromosome 22q11.2 **microdeletion** involves deletion of genes residing in adjacent loci. This results in variable phenotypes including **DiGeorge syndrome** (cardiac anomalies, hypoplastic/absent thymus, hypocalcemia) and **velocardiofacial syndrome** (cleft palate, cardiac anomalies, dysmorphic facies); the latter is exemplified in this patient.

Defective **neural crest migration** into derivatives of the **third** and **fourth** pharyngeal pouches results in maldevelopment of the thymus and parathyroid as well as subsequent T-cell deficiency and hypocalcemia. Cardiac defects include interrupted aortic arch and tetralogy of Fallot (described in this patient). Dysmorphic facial features include orbital hypertelorism, short palpebral fissures and short philtrum, cleft palate, and bifid uvula. In **fluorescence in situ hybridization** (the gold standard test), genes of interest are hybridized with fluorescently labeled DNA probe. Lack of fluorescent signal is indicative of a microdeletion.

(Choice A) Kartagener syndrome results from immotile cilia due to an autosomal recessive microtubular defect in the dynein arm. It results in infertility, situs inversus, chronic sinusitis, and bronchiectasis.

(Choice C) Marfan syndrome, a fibrillin defect, causes cystic medial necrosis of the aorta and joint hyperextensibility. It is not associated with a cleft palate, but rather with a high-arched palate with crowded teeth and a narrow face.

(Choice D) Microdeletion syndrome due to genomic imprinting includes Prader-Willi syndrome (PWS) and Angelman syndrome (AS). In PWS, paternal genes are deleted (15q-) and maternal genes are silenced, resulting in short stature, obesity, hypotonia, and hypogonadism. In AS,

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(Choice E) Tuberous sclerosis involves defective tumor suppressor gene-coded proteins hamartin (*TSC1*) and tuberin (*TSC2*), and is characterized by cutaneous angiofibromas, brain hamartomas, and cardiac rhabdomyomas.

(Choice F) Friedrich ataxia (GAA repeat) is characterized by spinocerebellar degeneration and spinal ataxia. It is not associated with facial or palatal malformations. Other examples of trinucleotide repeats include Fragile X (CGG) and myotonic dystrophy (CTG).

Educational objective:
Chromosome 22q11.2 microdeletion results in DiGeorge syndrome (cardiac anomalies, hypoplastic or absent thymus, and hypocalcemia) and velocardiofacial syndrome (cleft palate, cardiac anomalies, dysmorphic facies). Fluorescence in situ hybridization is the "gold standard" for

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References

- 22q11.21 deletion syndromes: a review of proximal, central, and distal deletions and their associated features.

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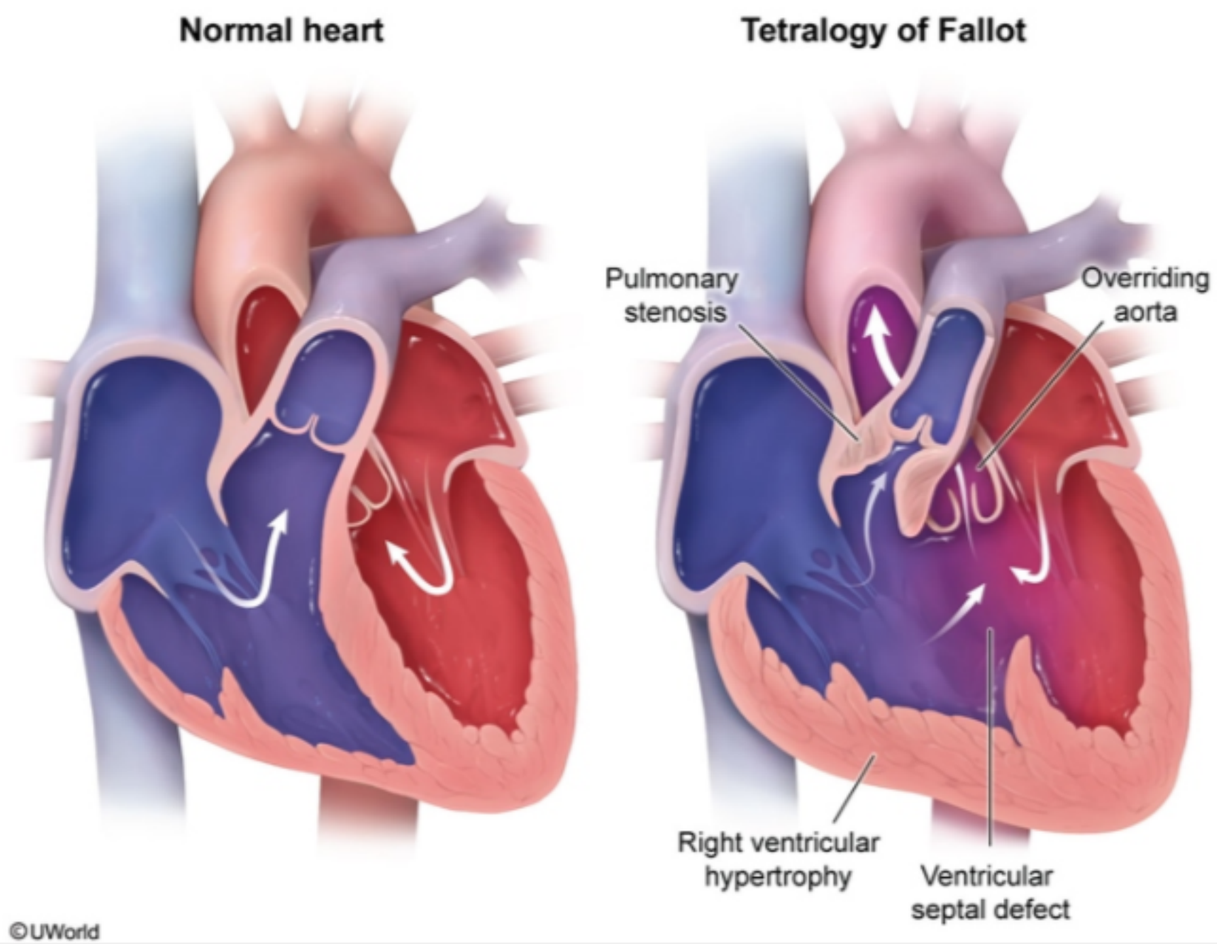

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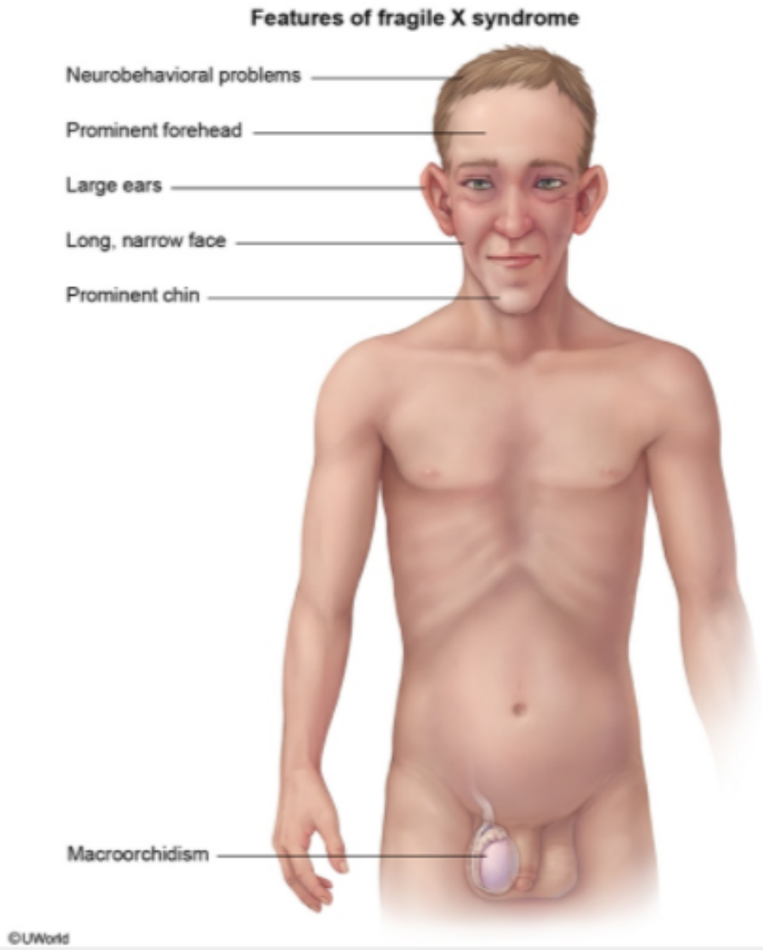

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(Choice A) Kartagener syndrome results from immotile cilia due to an autosomal recessive microtubular defect in the dynein arm. It results in infertility, situs inversus, chronic sinusitis, and bronchiectasis.

(Choice C) Marfan syndrome, a fibrillin defect, causes cystic medial necrosis of the aorta and joint hyperextensibility. It is not associated with a cleft palate, but rather with a high-arched palate with crowded teeth and a narrow face.

(Choice D) Microdeletion syndrome due to genomic imprinting includes Prader-Willi syndrome (PWS) and Angelman syndrome (AS). In PWS, paternal genes are deleted (15q-) and maternal genes are silenced, resulting in short stature, obesity, hypotonia, and hypogonadism. In AS, maternal genes are deleted (15q-) and paternal genes are silenced. Patients have microcephaly, ataxia, hand flapping movements, and frequent laughter ("happy puppet").

(Choice E) Tuberous sclerosis involves defective tumor suppressor gene-coded proteins hamartin (*TSC1*) and tuberin (*TSC2*), and is characterized by cutaneous angiofibromas, brain hamartomas, and cardiac rhabdomyomas.

(Choice F) Friedrich ataxia (GAA repeat) is characterized by spinocerebellar degeneration and spinal ataxia. It is not associated with facial or palatal malformations. Other examples of trinucleotide repeats include Fragile X (CGG) and myotonic dystrophy (CTG).

Educational objective:
Chromosome 22q11.2 microdeletion results in DiGeorge syndrome (cardiac anomalies, hypoplastic or absent thymus, and hypocalcemia) and velocardiofacial syndrome (cleft palate, cardiac anomalies, dysmorphic facies). Fluorescence in situ hybridization is the "gold standard" for detecting a microdeletion.

References

- 22q11.21 deletion syndromes: a review of proximal, central, and distal deletions and their associated features.
- Velocardiofacial syndrome, DiGeorge syndrome: the chromosome 22q11.2 deletion syndromes.

Genetics	Miscellaneous (Multisystem)	Digeorge syndrome
Subject	System	Topic

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A newborn is examined immediately after an induced vaginal delivery for fetal growth retardation. On visual inspection, the infant has low-set ears, a small mandible, and a prominent occiput. The neonate has a weak cry and increased tone of the extremities, including clenched hands with second and fifth digits on top of the third and fourth digits. Cardiac auscultation reveals a harsh, IV/VI holosystolic murmur heard best at the left sternal border. The infant is transferred to the neonatal intensive care unit for further workup and management. Which of the following is the most likely chromosomal abnormality in this infant?

A. 5p deletion

B. 22q11 deletion

C. 47, XX, +13

D. 47, XX, +18

E. 47, XX, +21

Submit

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- A. 5p deletion (7%)
- B. 22q11 deletion (7%)
- C. 47, XX, +13 (13%)
- ✓ D. 47, XX, +18 (64%)
- E. 47, XX, +21 (6%)

Omitted
Correct answer
D

64%
Answered correctly

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03/12/2020
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Explanation

Trisomy 18 (Edwards syndrome)

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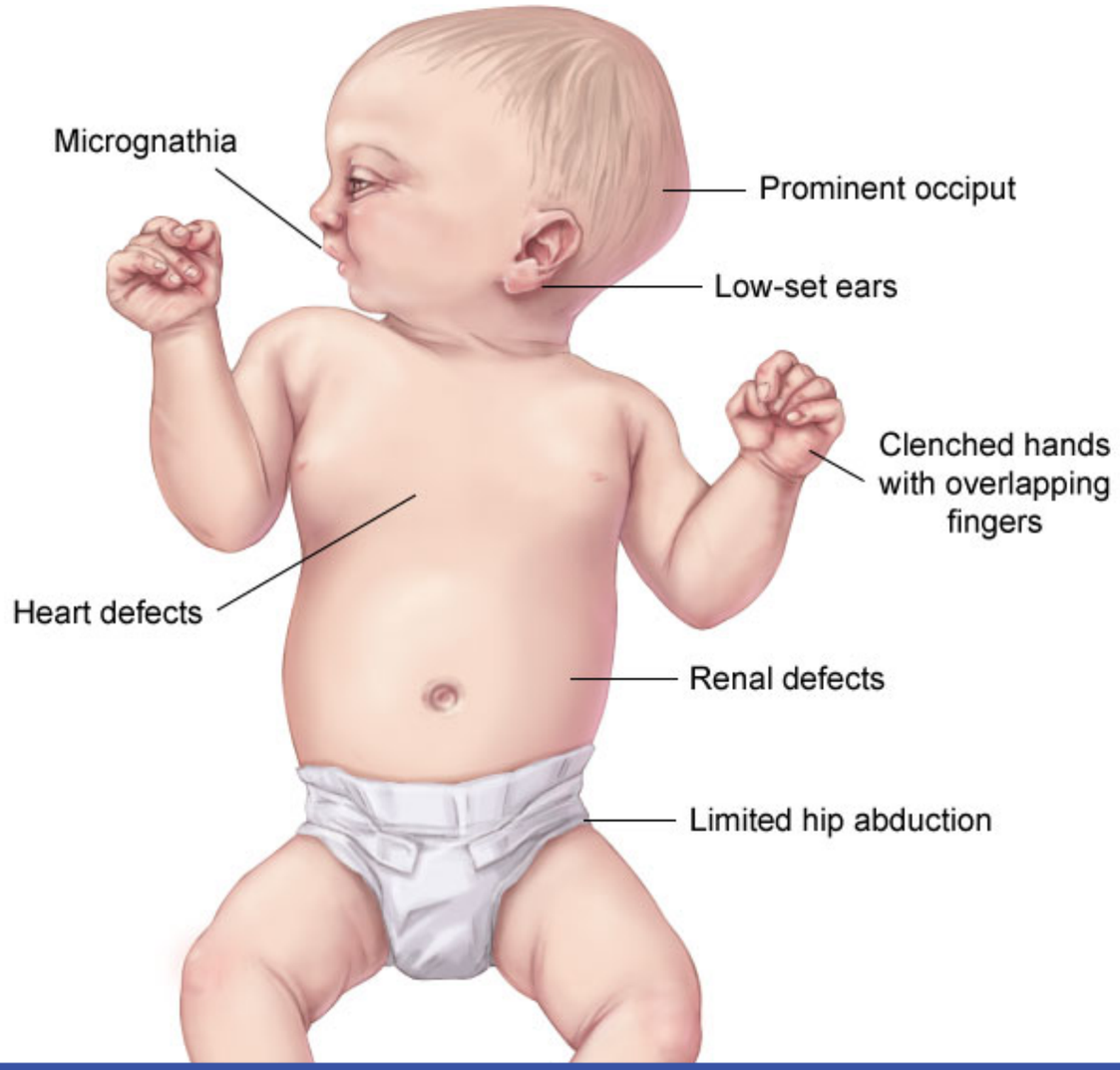
Trisomy 18 (Edwards syndrome)



This patient has **trisomy 18 (Edwards syndrome)**, in which a complete extra copy of chromosome 18 is inherited as a result of **meiotic nondisjunction**. This error in oocyte division occurs prior to ovulation and fertilization and increases with maternal age ≥35.

Dysmorphic features include micrognathia, low-set ears, prominent occiput, and **rocker bottom feet**. Patients have significant hypertonia, including **clenched hands** with **overlapping fingers**. Anomalies of cardiac (eg, **ventricular septal defect**, patent ductus arteriosus), genitourinary (eg, horseshoe kidney), and gastrointestinal (eg, Meckel's diverticulum, malrotation) systems are characteristic. Prenatal ultrasound findings include fetal growth restriction, as seen in this patient. The majority of those affected die in utero; half of livebirths die by age 2 weeks. Surviving patients have severe intellectual disability.

(Choice A) Cri-du-chat syndrome (5p deletion) presents with a weak or "cat-like" cry as well as hypotonia, failure to thrive, and developmental delay. Phenotypic features include microcephaly, low-set ears, hypertelorism, and a broad nasal bridge.

(Choice B) Features of DiGeorge syndrome (22q11 deletion) include aortic arch anomalies, thymic hypoplasia/aplasia, and hypocalcemia (parathyroid gland underdevelopment). Phenotypically, neonates can present with hypertelorism, low-set ears, micrognathia, and cleft palate.

(Choice C) Trisomy 13 (Patau syndrome) presents with midline facial defects (eg, holoprosencephaly, cleft lip/palate), musculoskeletal abnormalities (eg, polydactyly), and gastrointestinal anomalies (eg, omphalocele, umbilical hernia). Trisomy 13 is notably not associated with overlapping fingers.

(Choice E) Trisomy 21 (Down syndrome) is the most common autosomal trisomy. Classic findings include a flat facial profile, upslanting palpebral fissures, low-set small ears, single transverse palmar crease, and hypotonia.

Educational objective:

4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33

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Educational objective:
Trisomy 18, or Edwards syndrome, is most commonly the result of meiotic nondisjunction due to advanced maternal age. Key findings include fetal growth retardation, hypertonia (clenched hands with overlapping fingers), rocker bottom feet, and cardiac/gastrointestinal/renal defects.

References

- The trisomy 18 syndrome.

Genetics Miscellaneous (Multisystem) Trisomy 18

Dysmorphic features include micrognathia, low-set ears, prominent occiput, and **rocker bottom feet**. Patients have significant hypertonia, including **clenched hands** with **overlapping fingers**. Anomalies of cardiac (eg, **ventricular septal defect**, patent ductus arteriosus), genitourinary (eg, horseshoe kidney), and gastrointestinal (eg, Meckel's diverticulum, malrotation) systems are characteristic. Prenatal ultrasound findings include fetal growth restriction, as seen in this patient. The majority of those affected die in utero; half of livebirths die by age 2 weeks. Surviving patients have severe intellectual disability.

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References

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Genetics	Miscellaneous (Multisystem)	Trisomy 18
Subject	System	Topic

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Dysmorphic features include micrognathia, low-set ears, prominent occiput, and **rocker bottom feet**. Patients have significant hypertonia,

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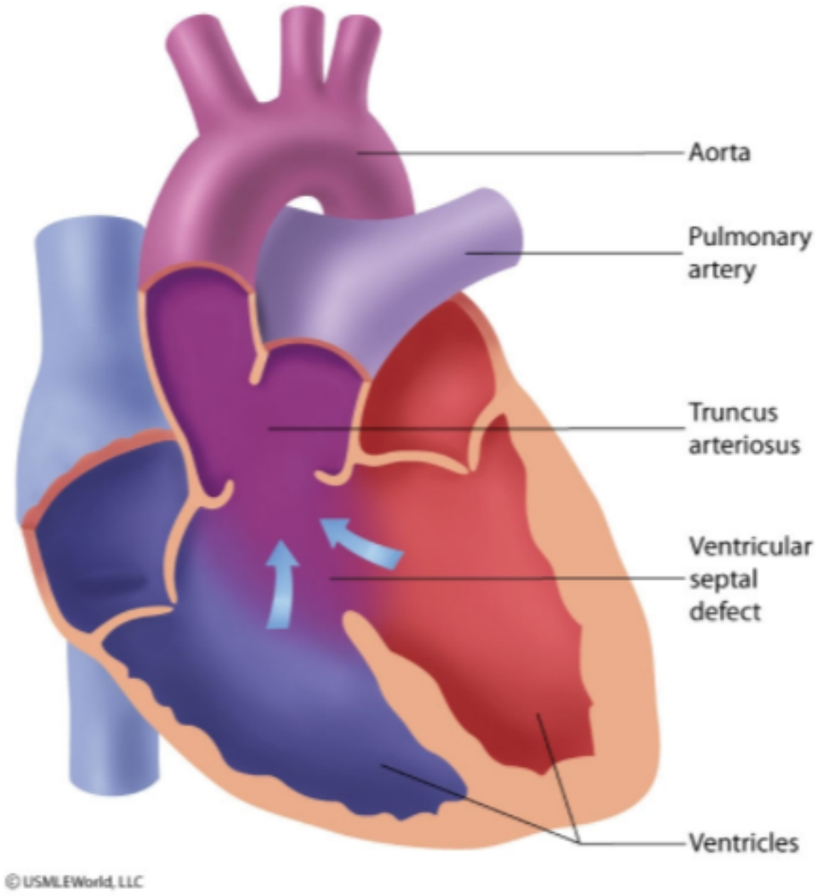
Truncus arteriosus



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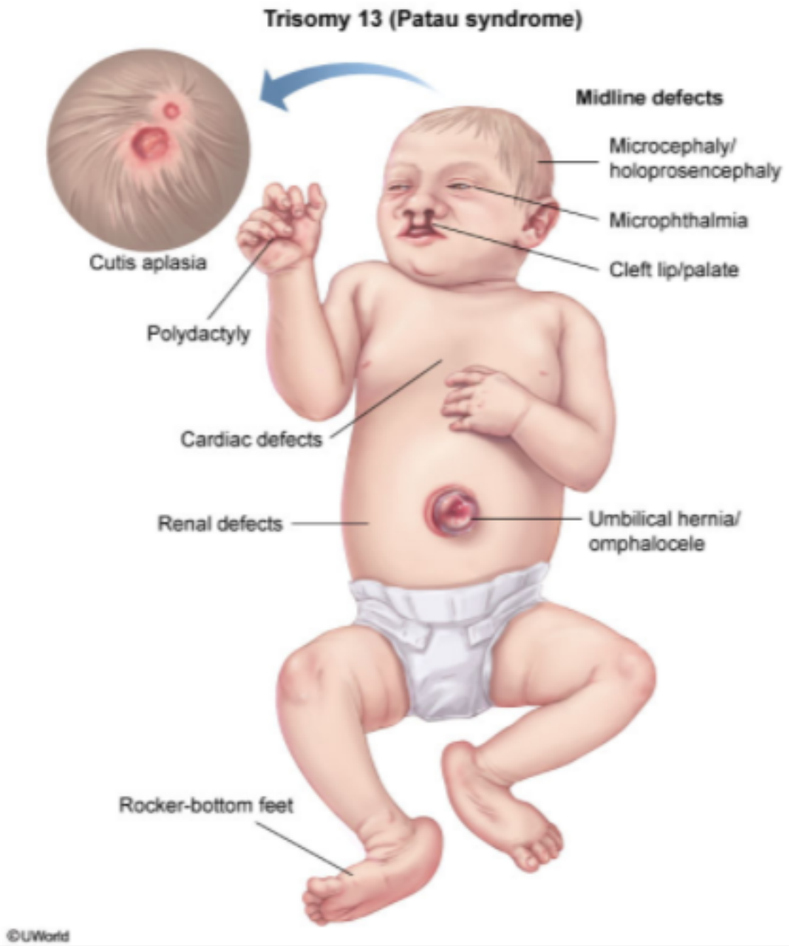

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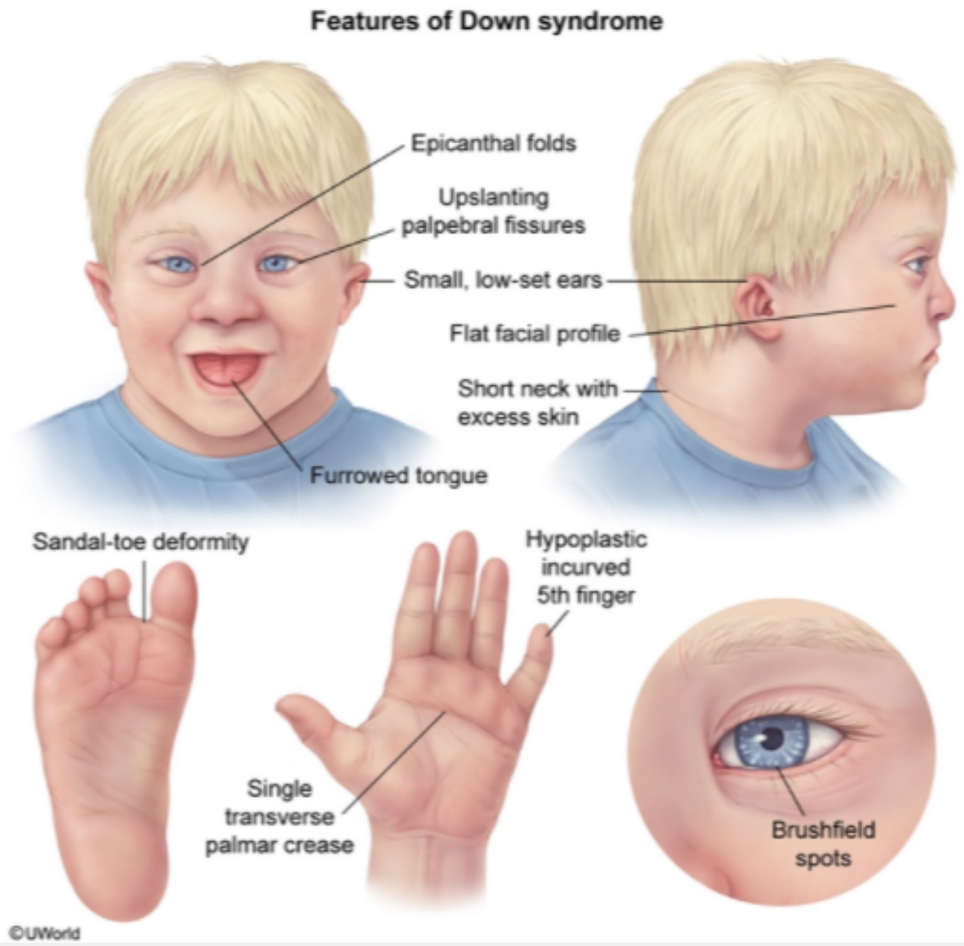

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A 23-year-old man is being evaluated for myoclonic epilepsy of recent onset. The episodes are short-lived and triggered by startle. Physical examination reveals proximal muscle weakness. Gomori trichrome stain of a muscle biopsy specimen shows muscle fibers with a blotchy red appearance. No family history is available because the patient is adopted. What is the probability that this patient's one offspring will inherit the disease?

- A. 100%
- B. 75%
- C. 50%
- D. 25%
- E. 0%

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A. 100% (5%)
B. 75% (2%)
C. 50% (22%)
D. 25% (14%)
✓ E. 0% (54%)

Omitted
Correct answer
E

54%
Answered correctly

02 secs
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02/03/2020
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Explanation

Blotchy red muscle fibers on Gomori trichrome stain are characteristic of the mitochondrial myopathies. In these conditions, abnormal mitochondria accumulate under the sarcolemma of muscle fibers. The fibers have an irregular shape and size on cross section. For this reason, the mitochondrial myopathies are also known as the "red ragged fiber" diseases. Electron microscopy of the affected muscle reveals an increased number of enlarged, abnormally shaped mitochondria.

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The most important mitochondrial myopathies are myoclonic epilepsy with ragged red fibers (MERRF, described in this vignette), Leber optic neuropathy (blindness), and mitochondrial encephalopathy with stroke-like episodes and lactic acidosis (MELAS). Each of these diseases is the result of a mitochondrial gene mutation.

The mitochondrial diseases are caused by mutations, deletions or duplications of mtDNA. Because sperm mitochondria do not pass into the ovum during fertilization, only maternal mitochondria are transmitted to the fetus. Mitochondrial diseases, therefore, have maternal inheritance. For this reason the male patient described in this vignette will not transmit the disease to his progeny.

(Choice B) No pure single-gene inherited disease shows 75% transmission. There may be 75% transmission for a disease with variable penetrance.

Individuals affected by a disease with autosomal dominant inheritance receive one copy of the abnormal gene from one parent. The chance that an affected person will transmit the disease to his/her child is 50% **(Choice C)** if the parent is heterozygous for the given disease. If the parent is homozygous, there is a 100% chance **(Choice A)** of transmission.

(Choice D) Autosomal recessive diseases occur when the individual inherits two copies of the mutated gene (one from each parent). If both parents are carriers, there is a 25% chance that the child will be affected.

Educational Objective:
"Red ragged" muscle fibers are seen in mitochondrial diseases. Muscle fibers have this appearance because abnormal mitochondria accumulate under the sarcolemma. Mitochondrial diseases show maternal inheritance.

Genetics	Nervous System	Mitochondrial disorders
Subject	System	Topic

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Educational Objective:
"Red ragged" muscle fibers are seen in mitochondrial diseases. Muscle fibers have this appearance because abnormal mitochondria accumulate under the sarcolemma. Mitochondrial diseases show maternal inheritance.

Genetics	Nervous System	Mitochondrial disorders
Subject	System	Topic

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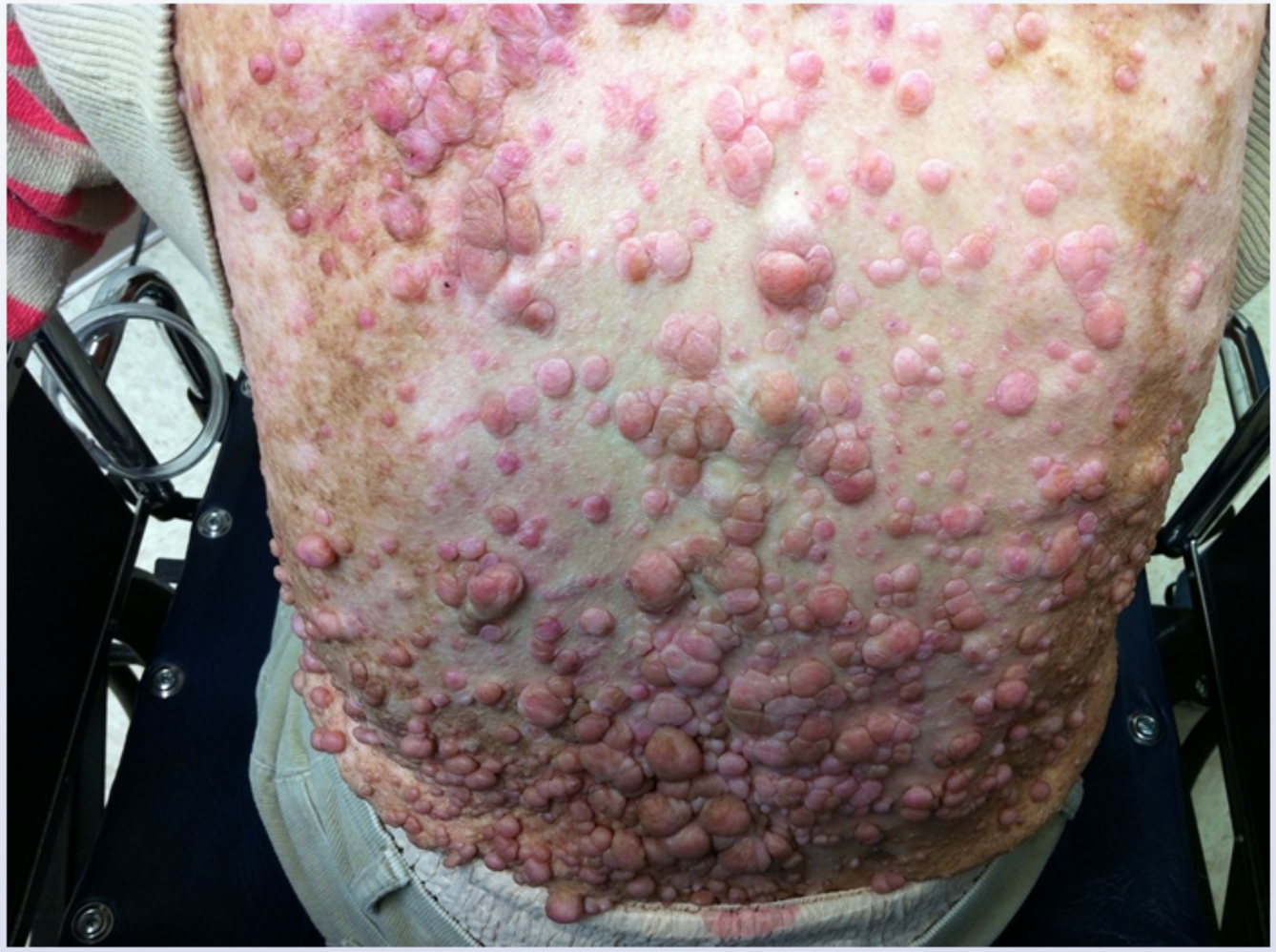
A 54-year-old man comes to the physician with recent-onset mild headaches and left leg weakness. The lesions seen on physical examination are shown in the image below.



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Which of the following inheritance patterns is this patient's disorder most likely to exhibit?

- A. Genomic imprinting
- B. Mitochondrial
- C. Multifactorial
- D. Single-gene autosomal dominant
- E. Single-gene autosomal recessive
- F. Single-gene X-linked

Submit

Which of the following inheritance patterns is this patient's disorder most likely to exhibit?

- A. Genomic imprinting (0%)
- B. Mitochondrial (1%)
- C. Multifactorial (5%)
- ✓ D. Single-gene autosomal dominant (71%)
- E. Single-gene autosomal recessive (17%)
- F. Single-gene X-linked (3%)

Omitted
Correct answer

71%
Answered correctly

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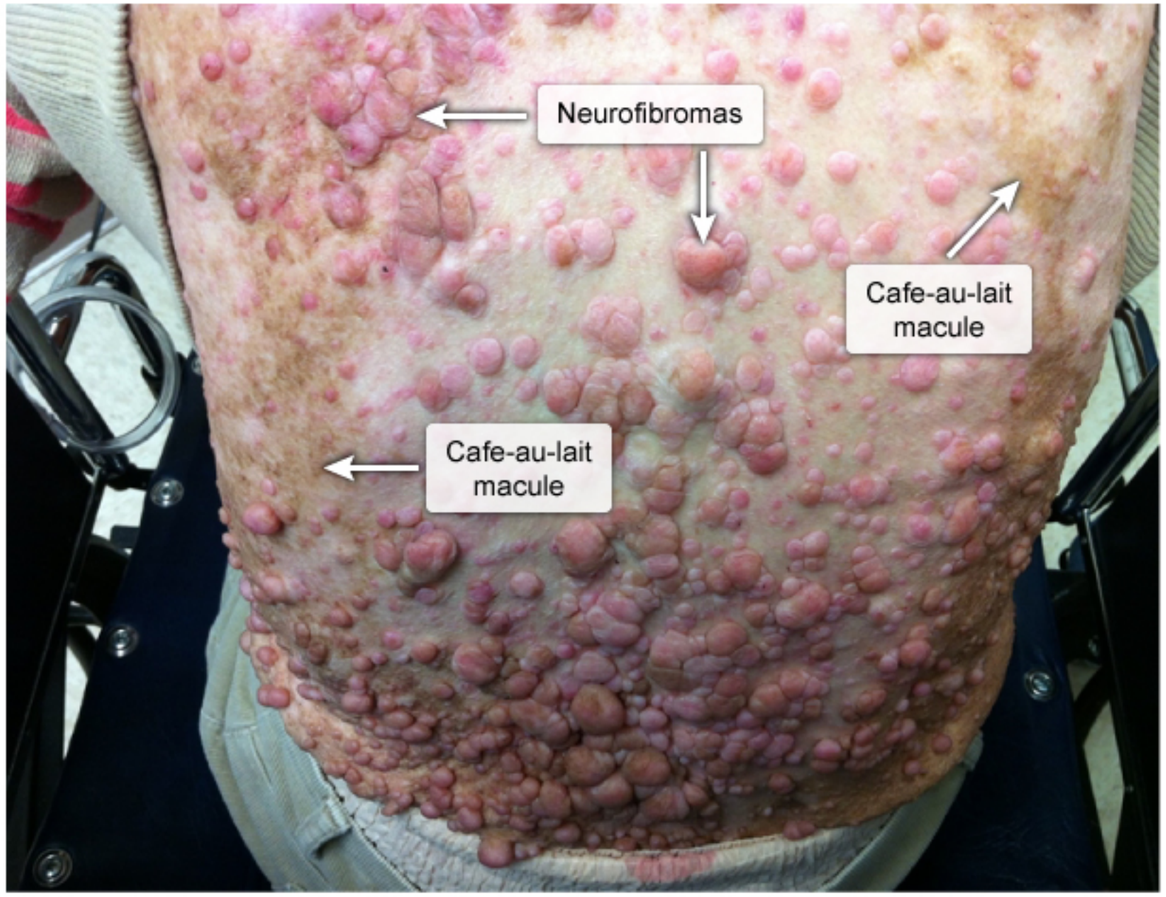
Neurofibromatosis type 1



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The numerous fleshy, dome-shaped or pedunculated lesions shown in the image are cutaneous neurofibromas, a hallmark of neurofibromatosis type 1 (NF-1). This autosomal dominant condition is caused by a mutation in the NF1 gene, located on chromosome 17.

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The numerous fleshy, dome-shaped or pedunculated lesions shown in the image are cutaneous neurofibromas, a hallmark of neurofibromatosis type 1 (NF-1). This autosomal dominant condition is caused by a mutation in the NF1 gene, located on chromosome 17.

NF-1 has high penetrance (most patients who inherit the gene develop the disease), but the presentation is highly variable. All or none of the following symptoms may be present in an individual who suffers from NF-1:

1. Skin: **Café-au-lait spots** (arrows) are hyperpigmented lesions with either smooth or irregular borders. The presence of axillary or inguinal freckles is another cutaneous feature of NF-1.
2. **Neurofibromas:** Short, sessile, or pedunculated lesions that vary in size. They are commonly multiple and distributed throughout the body.
3. Eye: Optic nerve gliomas may occur and cause visual loss. **Lisch nodules** are pigmented, asymptomatic hamartomas of the iris.
4. Bony abnormalities: These include sphenoid dysplasia, congenital **pseudoarthrosis**, and scoliosis.
5. Other associated tumors: Meningiomas, astrocytomas, gliomas, and pheochromocytomas. This patient's headaches and left leg weakness are probably the result of a brain tumor.

Educational objective:
Neurofibromatosis type 1 is a single-gene autosomal-dominant disorder. It occurs due to mutation of the NF1 gene located on chromosome 17. Café-au-lait spots, multiple neurofibromas, and Lisch nodules are the most common symptoms.

Genetics	Nervous System	Neurofibromatosis
Subject	System	Topic

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A 4-year-old boy is brought to the office due to a progressively worsening cough for the past 2 days that is productive of yellow sputum. A year ago, he was found to have bilateral lower-lobe pulmonary infiltrates on chest x-ray and was diagnosed with pneumonia. The patient has since had 2 additional episodes of pneumonia, each requiring antibiotics for improvement of symptoms. His current chest x-ray again reveals bilateral lower lobe infiltrates. Further testing shows a high chloride content in his sweat. Which of the following abnormalities is most likely to be seen in this patient?

A. Abnormal post-translational processing of a transmembrane protein

B. Decreased transcription of a transmembrane protein

C. Increased conductivity of a transmembrane chloride channel

D. Presence of a truncated transmembrane protein on the cell surface

E. Transmembrane protein with increased regulatory response to cAMP and ATP

Submit

A 4-year-old boy is brought to the office due to a progressively worsening cough for the past 2 days that is productive of yellow sputum. A year ago, he was found to have bilateral lower-lobe pulmonary infiltrates on chest x-ray and was diagnosed with pneumonia. The patient has since had 2 additional episodes of pneumonia, each requiring antibiotics for improvement of symptoms. His current chest x-ray again reveals bilateral lower lobe infiltrates. Further testing shows a high chloride content in his sweat. Which of the following abnormalities is most likely to be seen in this patient?

- ✓ A. Abnormal post-translational processing of a transmembrane protein (61%)
- B. Decreased transcription of a transmembrane protein (9%)
- C. Increased conductivity of a transmembrane chloride channel (9%)
- D. Presence of a truncated transmembrane protein on the cell surface (18%)
- E. Transmembrane protein with increased regulatory response to cAMP and ATP (1%)

Omitted
Correct answer
A

61%
Answered correctly

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Explanation

ΔF508 mutations & CFTR post-translational processing

Ribosome

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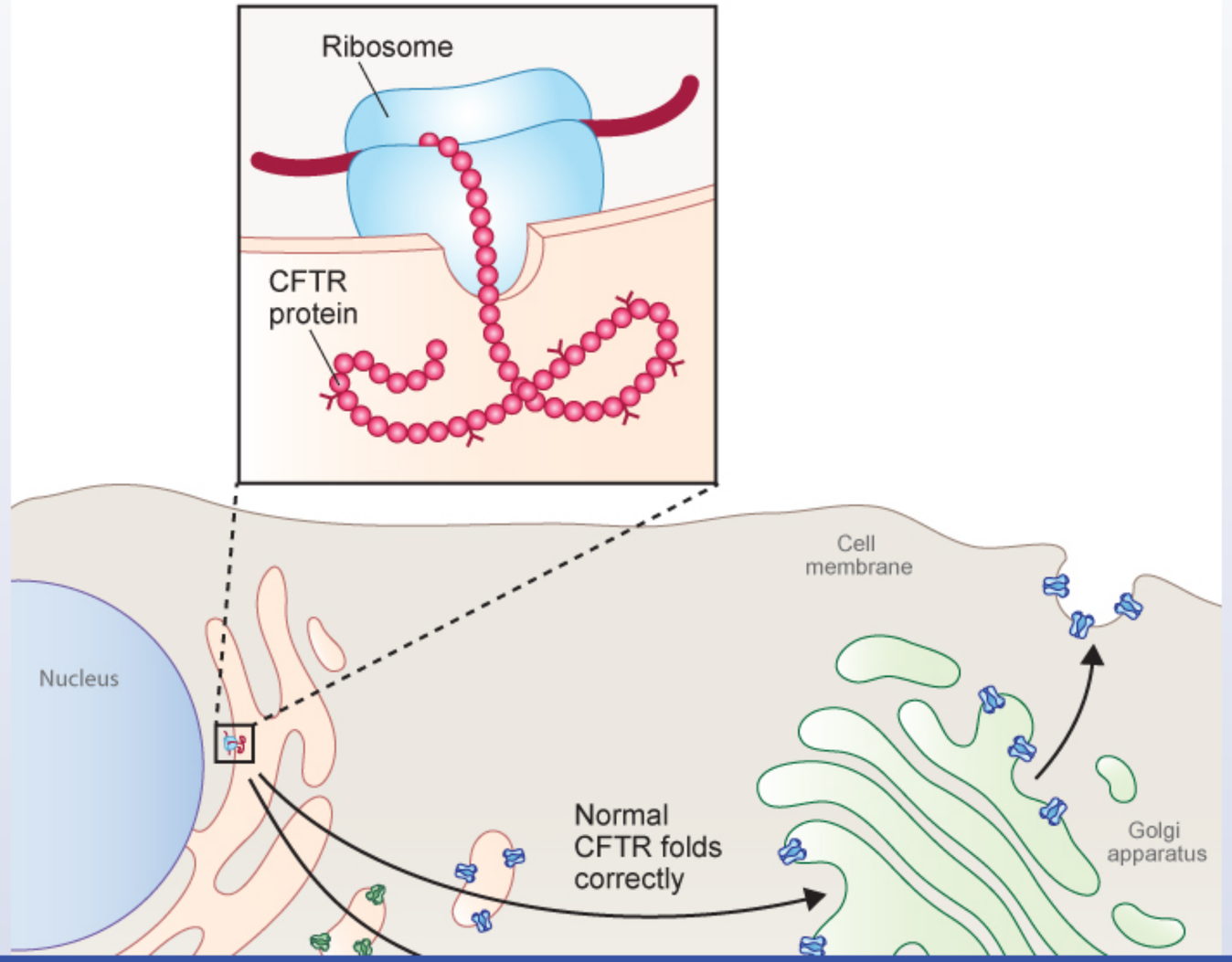
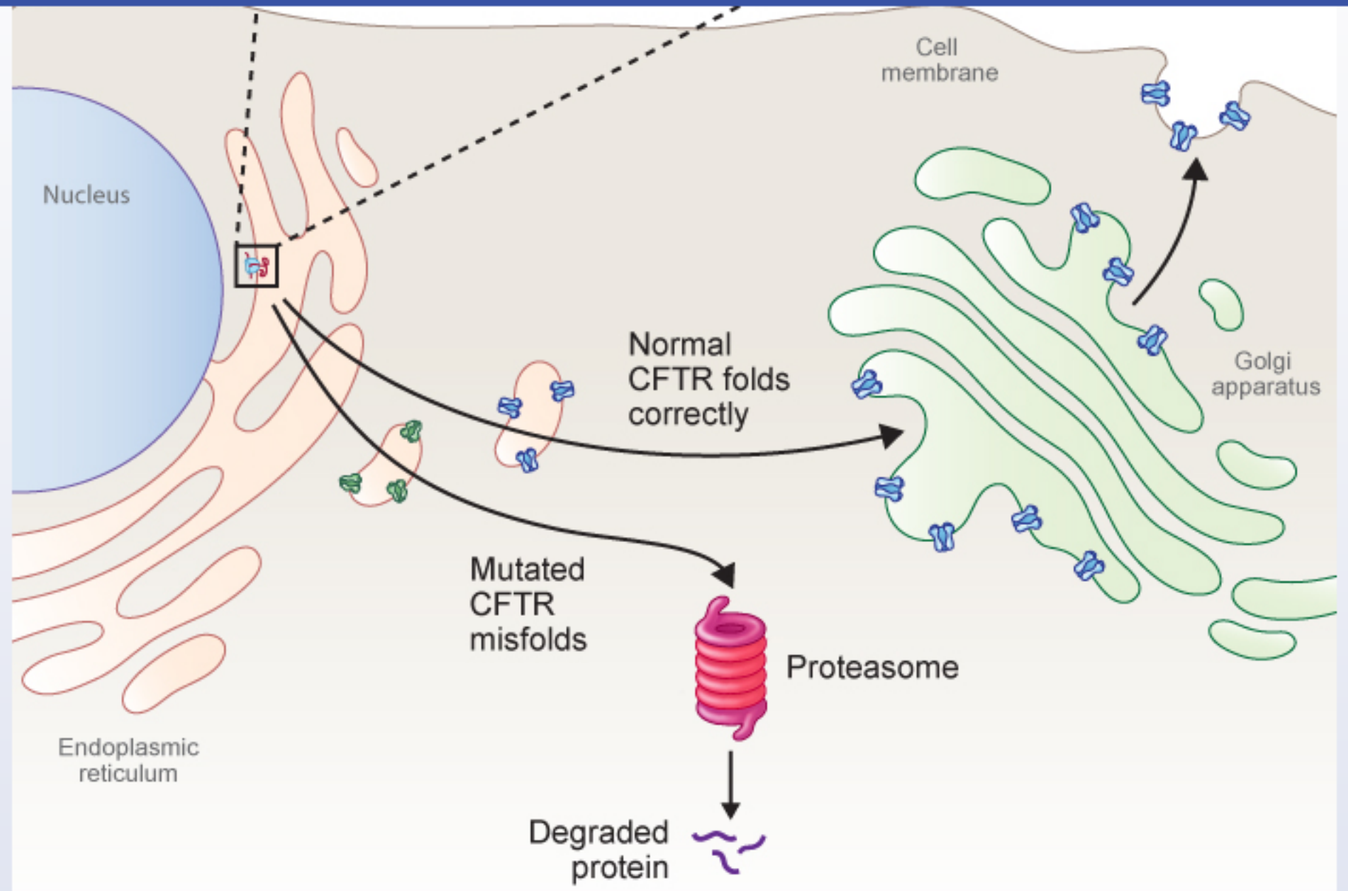
ΔF508 mutations & CFTR post-translational processing





CFTR = cystic fibrosis transmembrane conductance regulator.
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This patient most likely has cystic fibrosis (CF), an autosomal recessive disease characterized by recurrent **sinopulmonary infections**, pancreatic insufficiency, and malabsorption. It is caused by several different mutations that affect the CF transmembrane conductance regulator **(CFTR)** gene.

The **most common CFTR gene mutation** (found in approximately 70% of cases) is a 3-base pair deletion of phenylalanine at amino acid position

This patient most likely has cystic fibrosis (CF), an autosomal recessive disease characterized by recurrent **sinopulmonary infections**, pancreatic insufficiency, and malabsorption. It is caused by several different mutations that affect the CF transmembrane conductance regulator **(CFTR)** gene.

The **most common CFTR gene mutation** (found in approximately 70% of cases) is a 3-base pair deletion of phenylalanine at amino acid position 508 (**ΔF508**). This mutation causes **impaired post-translational processing** (eg, improper folding and glycosylation) of CFTR, which is detected by the endoplasmic reticulum. As a result, the abnormal protein is targeted for proteasomal degradation, preventing it from reaching the cell surface. Certain drugs (eg, lumacaftor) can partially correct this folding defect, leading to expression of functional CFTR.

(Choice B) Decreased production of functionally normal CFTR (eg, reduced messenger RNA or protein stability) often causes a milder form of the disease with normal sweat chloride levels that may not be diagnosed until adulthood.

(Choice C) Mutations affecting regulation of chloride ion conduction through a CFTR protein also result in CF. However, they result in decreased chloride conductivity and are less common than the ΔF508 mutation.

(Choice D) Mutations causing premature termination of the transmembrane protein (eg, nonsense, frameshift) also lead to a complete absence of membrane-bound CFTR as the truncated protein is typically recognized and degraded. These mutations are more common in the Ashkenazi Jewish population.

(Choice E) CFTR is an ATP-gated chloride channel activated by cAMP-mediated phosphorylation. Mutations that reduce the ability of the channel to open can also cause CF. The ΔF508 mutation, in addition to preventing proper trafficking to the cell surface, also reduces the regulatory effects of ATP and cAMP on channel opening.

Educational objective:
Cystic fibrosis (CF) is most commonly due to a 3-base pair deletion in the CF transmembrane conductance regulator (CFTR) gene at amino acid position 508 (ΔF508). This mutation impairs post-translational processing of CFTR, resulting in shunting of CFTR toward the proteasome, with complete absence of the protein on the cell surface. Elevated sweat chloride concentrations are found in most patients with CF.

References

- Protein processing and inflammatory signaling in cystic fibrosis: challenges and therapeutic strategies.

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(Choice E) CFTR is an A

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Educational objective:

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- Protein processing and inflammatory signaling in cystic fibrosis: challenges and therapeutic strategies.

Exhibit Display

Features of cystic fibrosis	

Pathogenesis	• Autosomal recessive mutation (ΔF508) impairs CFTR function
	• Decreased water content causes thick, viscous mucus:
	  ◦ Chronic airway obstruction
	  ◦ Gastrointestinal malabsorption

Clinical manifestations	• Chronic, productive cough • Recurrent sinopulmonary infections (especially *Staphylococcus aureus* & *Pseudomonas aeruginosa*) • Pancreatic insufficiency • Male infertility (bilateral absence of vas deferens)
Diagnosis	• Elevated sweat chloride levels • Nasal potential difference measurements • Genetic testing for *CFTR* mutations
CFTR = cystic fibrosis transmembrane conductance regulator.	

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A 14-year-old boy experiences severe, prolonged bleeding following a tooth extraction. He also has a history of multiple episodes of painful joint swelling following minor trauma. His parents have no bleeding problems. Evaluation shows that the patient has an inherited disorder and that one of his parents is a genetic carrier. His older sister, who does not have this condition, is pregnant. She does not know the sex of her child. She asks about the risk that her child will be affected. Which of the following is the best estimate that this child will have the disease?

A. Near 0
B. 1/2
C. 1/4
D. 1/8
E. 1/16
F. 1/32

Submit

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- A. Near 0 (10%)
- B. 1/2 (8%)
- C. 1/4 (29%)
- ✓ D. 1/8 (45%)
- E. 1/16 (5%)
- F. 1/32 (1%)

Omitted
Correct answer
D

45%
Answered correctly

02 secs
Time Spent

04/05/2020
Last Updated

Explanation

Hemophilia inheritance probability

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Hemophilia inheritance probability

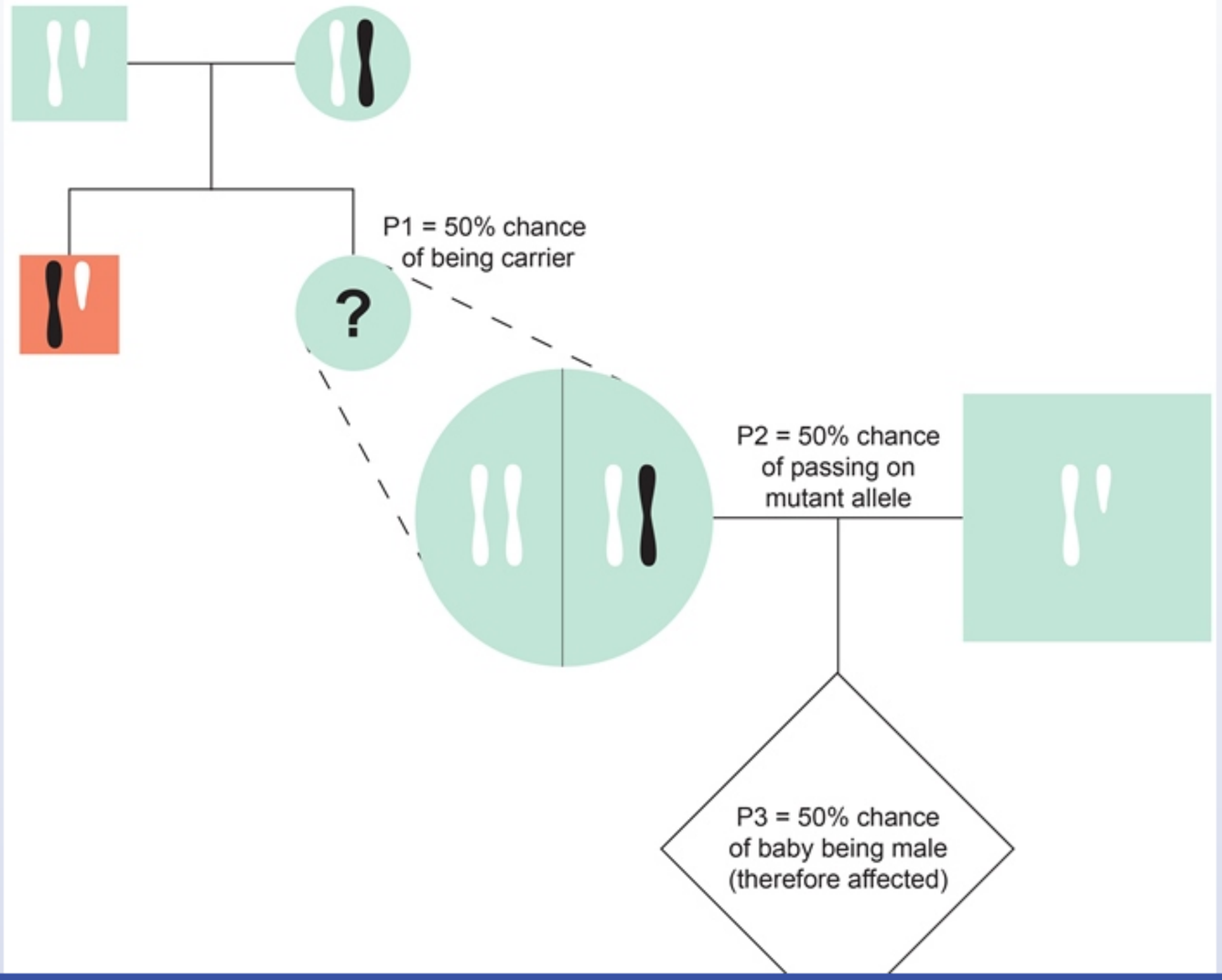
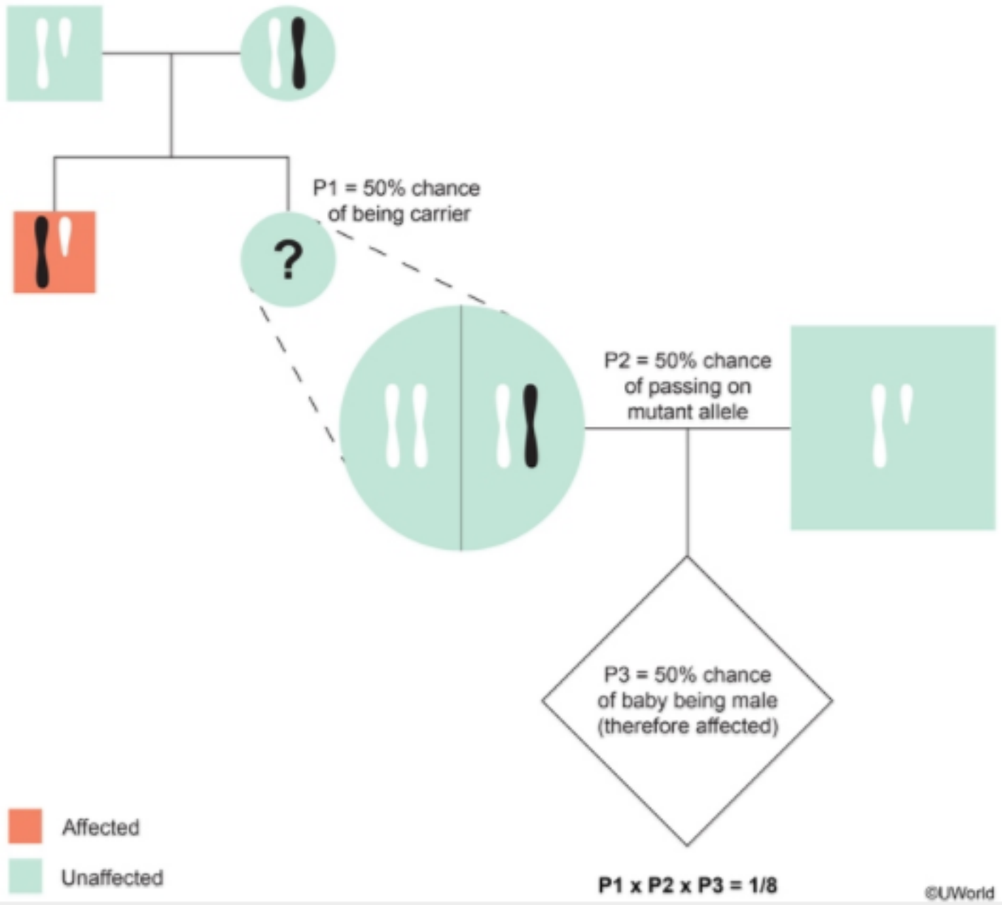


Exhibit Display

Hemophilia inheritance probability



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This patient is a boy with excessive bleeding and hemarthroses, suggesting a diagnosis of **hemophilia** A or B. Both diseases are X-linked recessive coagulation factor deficiencies. The probability that his sister will give birth to an affected child can be calculated by multiplying the following probabilities:

- The probability (p1) that the sister is a **carrier** = 0.5. The patient's father does not carry the mutation on his X chromosome because he would be affected by the disease if he did. That means the mother carries the mutation on 1 of her 2 X chromosomes. This gives the daughter a 50% chance of having inherited the mutated X chromosome and therefore being a carrier.
- The probability (p2) that the offspring of a female carrier will **inherit** the X chromosome with the hemophilia gene = 0.5. Assuming the daughter is a carrier, the probability of passing on the mutant allele is 50% as only 1 of her 2 X chromosomes is passed to her offspring.
- The probability (p3) that his sister will have a **boy** = 0.5. If the sister's child is female, the child could be a carrier of the disease but would not be affected by it. If a male child inherits the mutated X chromosome, he will have the disease.

The probability that the sister will have an affected son is the probability that all 3 of the above events will take place (ie, the product of their individual probabilities): p1 x p2 x p3 = 1/2 x 1/2 x 1/2 = 1/8.

Educational objective:
Given phenotypically normal parents, the probability that a female sibling of a male affected by an X-linked recessive disease will give birth to an affected child is 1/8.

Genetics	Hematology & Oncology	X linked inheritance
Subject	System	Topic

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A study is undertaken to map the HLA-DQ loci in a population with a high incidence of celiac sprue. High-resolution HLA typing of the DQA1 and DQB1 loci is performed using polymerase chain reaction sequencing. The frequency of the DQA1*0501-DQB1*0201 haplotype, strongly implicated in autoimmunity, is found to be 0.2. However, in the same population, the frequency of the DQA1*0501 allele is 0.3 and the frequency of the DQB1*0201 allele is 0.2. Which of the following best explains the observed DQA1*0501-DQB1*0201 haplotype frequency in this population?

- A. Heteroplasmy
- B. Increased penetrance
- C. Linkage disequilibrium
- D. Pleiotropy
- E. Segregation

Submit

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- A. Heteroplasmy (11%)
- B. Increased penetrance (8%)
- ✓ C. Linkage disequilibrium (60%)
- D. Pleiotropy (13%)
- E. Segregation (7%)

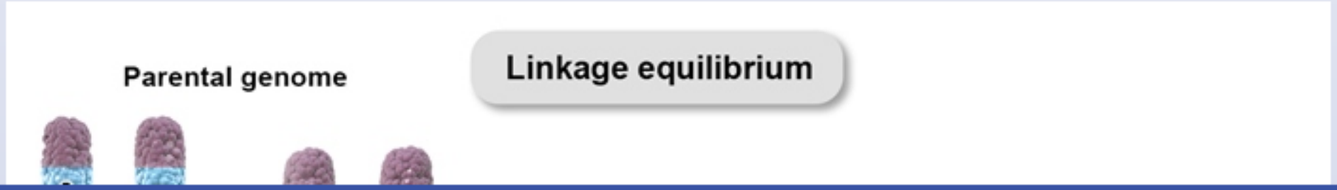
Omitted
Correct answer
C

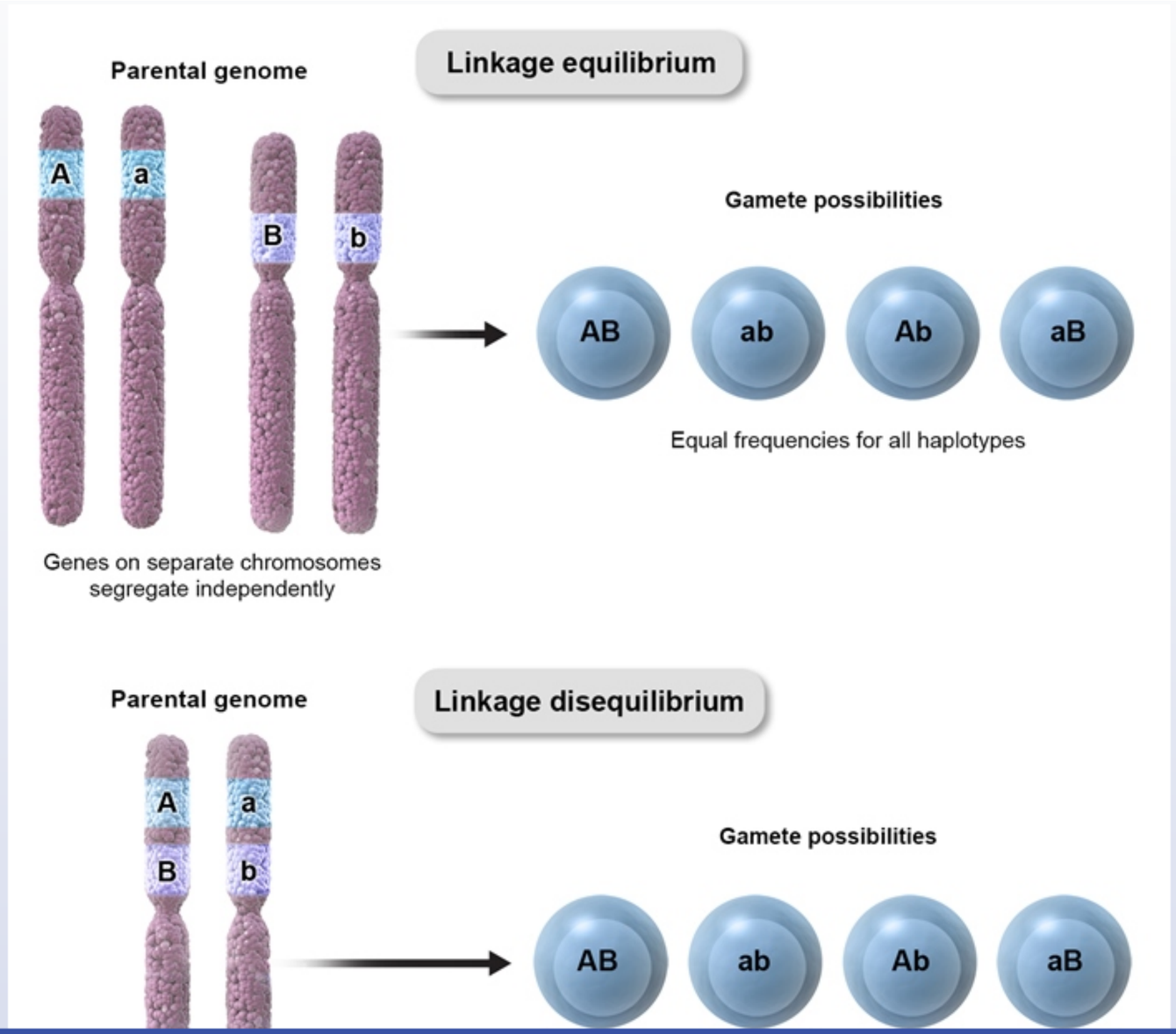
60%
Answered correctly

02 secs
Time Spent

02/17/2020
Last Updated

Explanation




Linkage equilibrium
Parental genome
A
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Genes on separate chromosomes segregate independently
Gamete possibilities
AB
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aB
Equal frequencies for all haplotypes
Linkage disequilibrium
Parental genome
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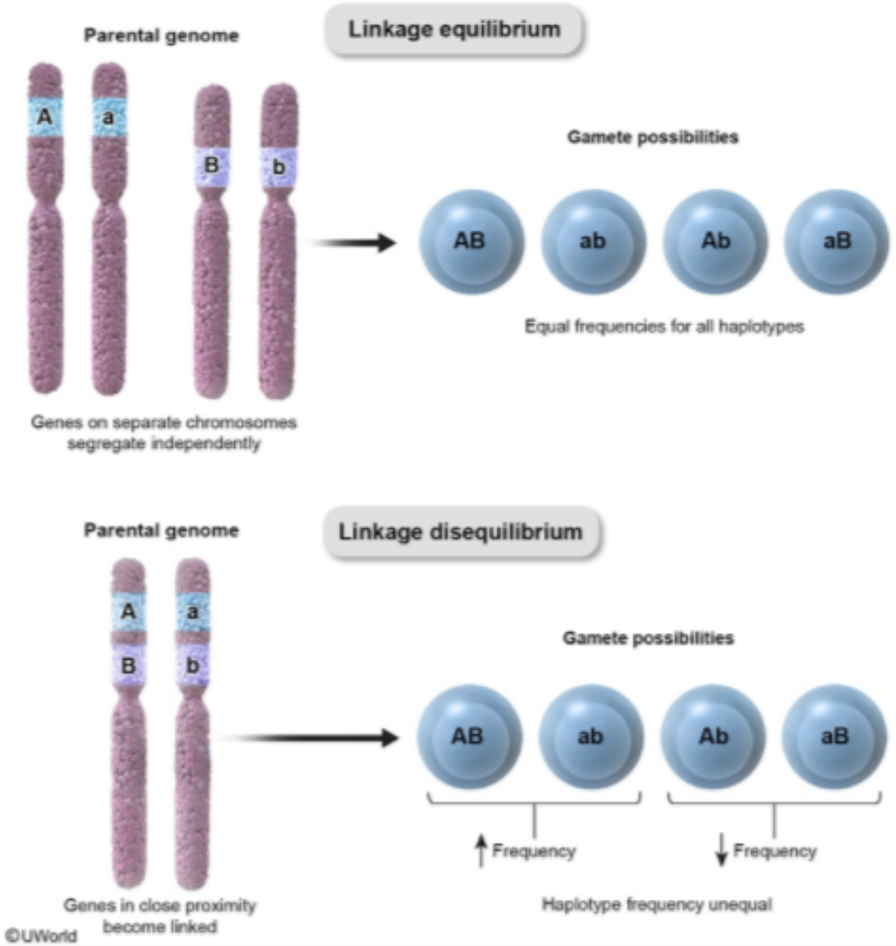
Exhibit Display



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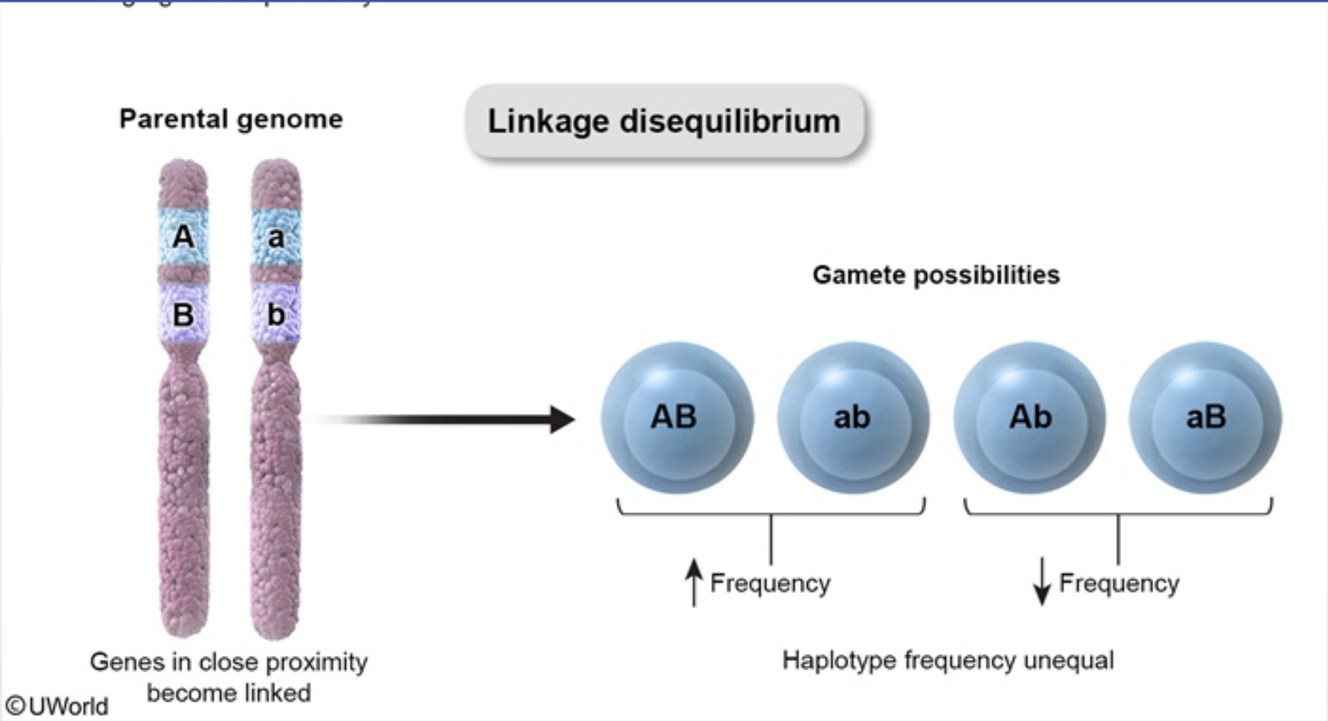

Two genetic loci are said to be in **linkage disequilibrium** when their respective alleles are **inherited together** in the same gamete (haplotype) **more or less often than expected** by chance alone given their corresponding allele frequencies. Although linkage disequilibrium is often the result of **physical proximity** of genes on the same chromosome, it does not always imply physical linkage between the allelic loci.

To estimate the expected probability of 2 alleles from separate loci appearing together, multiply their occurrence rates. Note that the Hardy-Weinberg principle (2pq) is not applicable when considering alleles at different loci.

DQA1*0501-DQB1*0201 haplotype frequency	= [Frequency of DQA1*0501] × [Frequency of DQB1*0201]
	= 0.3 × 0.2

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DQA1*0501-DQB1*0201 haplotype frequency	= [Frequency of DQA1*0501] × [Frequency of DQB1*0201]
	= 0.3 × 0.2
	= **0.06**

In this example, the observed frequency of both alleles being inherited together is **0.2**, which is greater than the expected frequency of 0.06; therefore, the population is said to be in linkage disequilibrium. This disequilibrium is explained by the close proximity of the HLA-DQA1 and HLA-DQB1 loci that code for α and β chains of class II major histocompatibility complex.

(Choice A) Heteroplasmy describes the presence of different mitochondrial genomes (eg, mutated and wild type) within a single cell. The severity of mitochondrial diseases is often related to the proportion of abnormal to normal mitochondria.

(Choice B) Penetrance is the proportion of people with a given genotype who express its associated phenotype. If all individuals with a given gene express its phenotype, that gene is said to have full penetrance.

(Choice D) Pleiotropy is the occurrence of multiple phenotypic manifestations, often in different organ systems, which result from a mutation in a single gene.

(Choice E) The law of segregation describes the phenomenon in which gametogenesis results in the separation of paired chromosomes so that the offspring inherit only half of each parent's genetic composition.

Educational objective:

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Educational objective:
Two allele loci are said to be in linkage disequilibrium when a pair of alleles are inherited together in the same gamete (haplotype) more often or less often than would be expected given random pairing. This most often occurs when the genes are in close physical proximity on the same chromosome.

References

- Gene polymorphisms, inflammatory diseases and cancer.
- Linkage disequilibrium and its expectation in human populations.

Genetics	Miscellaneous (Multisystem)	Linkage disequilibrium
Subject	System	Topic

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

A 16-year-old girl with a history of anemia since childhood is evaluated for a genetic abnormality after several members of her family are also found to be anemic. It is determined that she has a point mutation in the β globin gene, which has resulted in the substitution of guanine (G) with cytosine (C) in the mRNA sequence shown below.

Item 1 of 2

Which of the following cellular processes is most likely impaired due to this patient's gene mutation?

A. Co-translational protein targeting to endoplasmic reticulum

B. Initiation of translation

C. Peptide bond formation

D. Ribosomal translocation during polypeptide elongation

E. Termination of polypeptide synthesis

Submit

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		+1
Normal mRNA:	5' - - -	G C C G C C G C C A U G G U G C G C U U C C A C - - - 3'
Patient's mRNA:	5' - - -	G C C G C C C C C A U G G U G C G C U U C C A C - - - 3'

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Item 1 of 2

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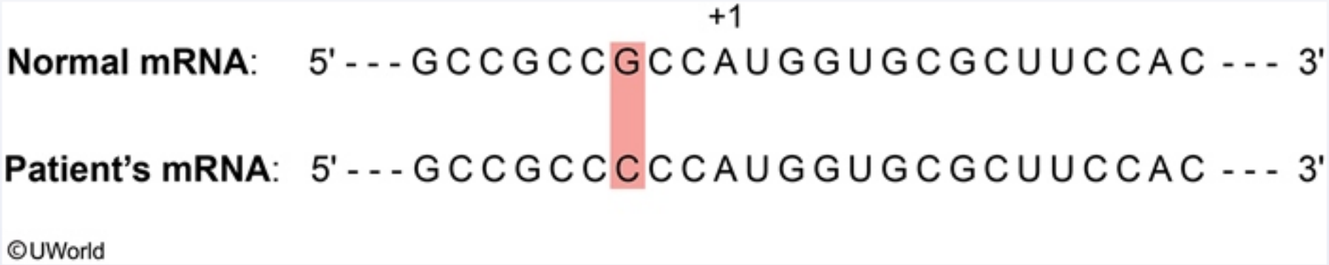

Item 1 of 2

Which of the following cellular processes is most likely impaired due to this patient's gene mutation?

- A. Co-translational protein targeting to endoplasmic reticulum (20%)
- ✓ B. Initiation of translation (45%)
- C. Peptide bond formation (15%)
- D. Ribosomal translocation during polypeptide elongation (12%)
- E. Termination of polypeptide synthesis (5%)

Omitted
Correct answer

45%
Answered correctly

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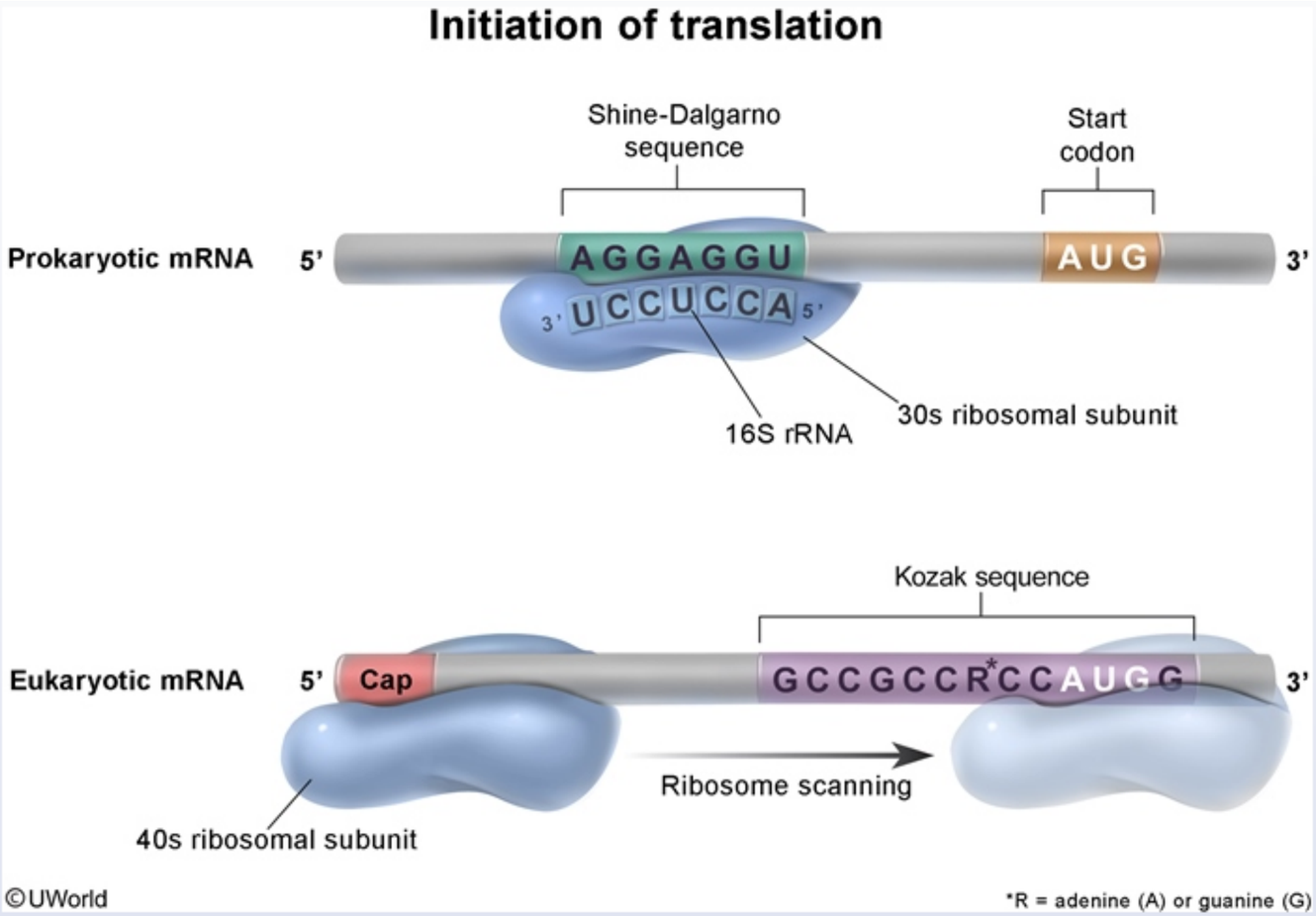
Time Spent

02/09/2020
Last Updated



This patient likely has β thalassemia due to an inherited β globin gene mutation in the Kozak sequence, a consensus sequence that helps start translation in eukaryotes. **Eukaryotic translation initiation** requires the assembly of ribosomal subunits (60S and 40S), mRNA, initiation factors, initiator tRNA charged with methionine, and guanosine-5'-triphosphate (GTP). The small ribosomal subunit (40S) initially binds to the 5' cap of mRNA and scans for the **methionine start codon (AUG)**. When this start codon is positioned near the beginning of an mRNA molecule and is surrounded by the Kozak consensus sequence, it serves as the initiator of translation.

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The **Kozak consensus sequence** is analogous to the Shine-Dalgarno sequence in *Escherichia coli*. It is defined by the following sequence: (gcc)gccRccAUGG, in which R is either adenine (A) or guanine (G). Among other factors, a purine (A or G) positioned 3 bases upstream from AUG appears to play a key role in this initiation process.

(Choice A) Co-translational protein targeting is mediated by the N-terminal amino acid sequence of an elongating polypeptide. This signal sequence is recognized by a signal recognition particle, which helps transport the protein to the rough endoplasmic reticulum.

(Choice C) Peptide bond formation is catalyzed by peptidyl transferase, an RNA enzyme ("ribozyme") that resides in the large ribosomal subunit. A defect in rRNA coding for ribosomes would be required to interfere with this process.

(Choice D) During polypeptide elongation, the ribosome moves 3 nucleotides toward the 3' end of mRNA, advancing peptidyl tRNA from the A site to the P site (translocation). Translocation is catalyzed by elongation factor 2 and requires GTP hydrolysis.

(Choice E) Termination of polypeptide synthesis occurs at stop codons. Mutations in stop codons (nonstop mutations) can result in continued and inappropriate translation of mRNA into the 3'-untranslated region, producing an extremely long, nonfunctional polypeptide.

Educational objective:
The Kozak consensus sequence occurs on eukaryotic mRNA and is defined by the following sequence: (gcc)gccRccAUGG, in which R is either adenine or guanine. This sequence helps initiate translation at the methionine start codon (AUG).

References

- Diversity of preferred nucleotide sequences around the translation initiation codon in eukaryote genomes.
- Beta+45 G --> C: a novel silent beta-thalassaemia mutation, the first in the Kozak sequence.

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- Beta+45 G --> C: a novel silent beta-thalassaemia mutation, the first in the Kozak sequence.
- Beta-thalassemia.

Genetics	Hematology & Oncology	Thalassemia
Subject	System	Topic

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Item 2 of 2

The patient's genetic defect has resulted in decreased β globin chain synthesis. Which of the following is most likely to be seen on laboratory testing?

A. Hyperchromia
B. Iron deficiency
C. Microcytosis
D. Red blood cell sickling
E. Spherocytosis

Submit

Item 2 of 2

The patient's genetic defect has resulted in decreased β globin chain synthesis. Which of the following is most likely to be seen on laboratory testing?

- A. Hyperchromia (3%)
- B. Iron deficiency (4%)
- ✓ C. Microcytosis (78%)
- D. Red blood cell sickling (8%)
- E. Spherocytosis (4%)

Omitted
Correct answer
C

78%
Answered correctly

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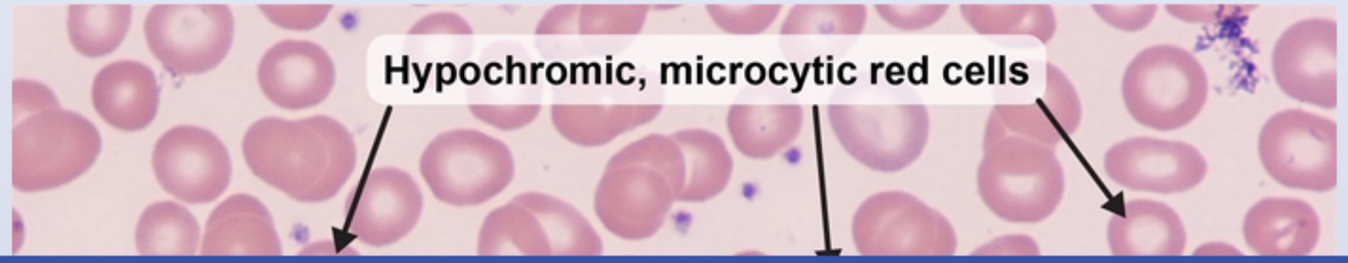
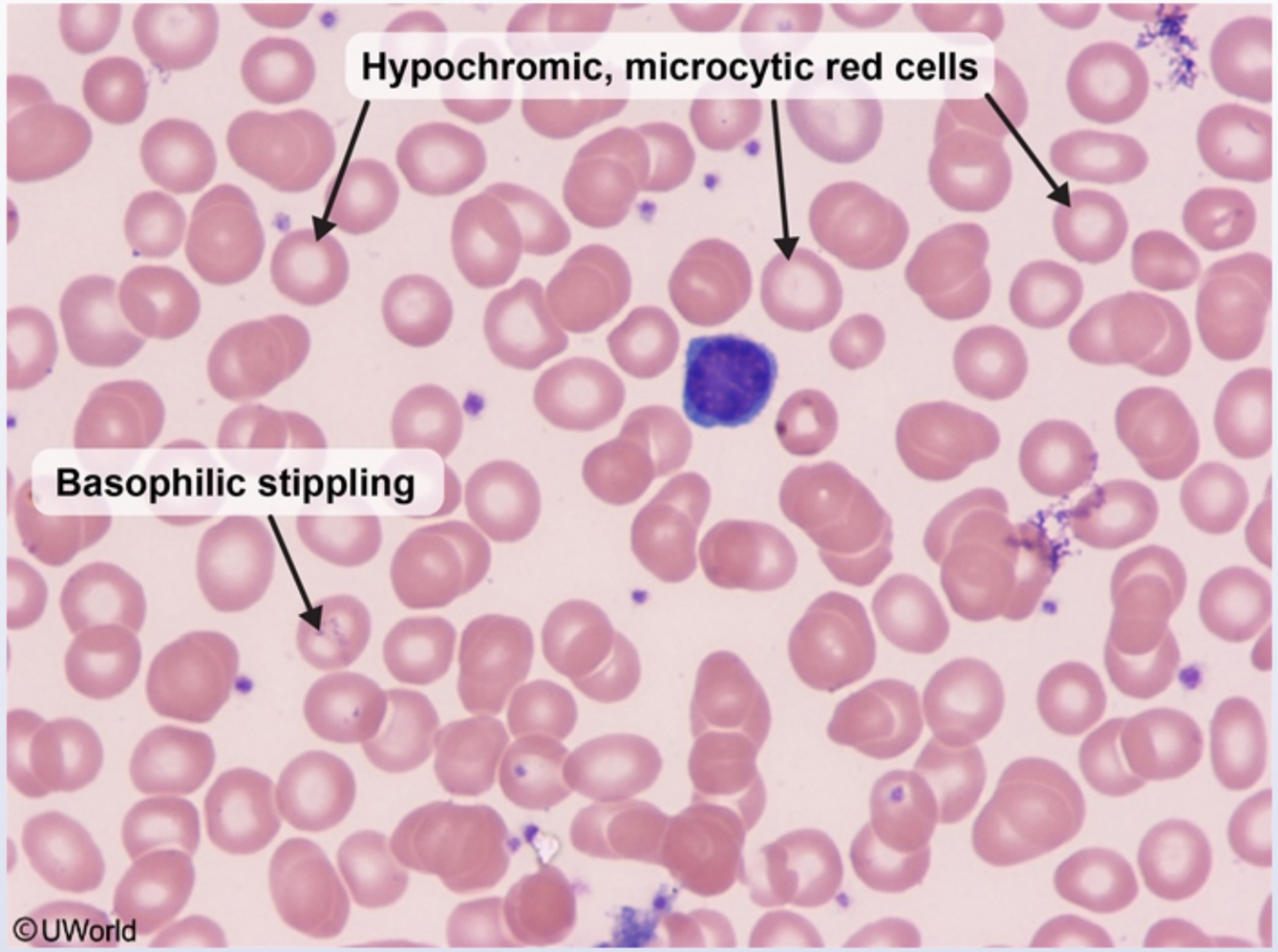
Time Spent

03/09/2020
Last Updated

Explanation





Patients with **β thalassemia** have decreased β globin chain synthesis, which causes **hypochromic, microcytic anemia** (mean corpuscular volume <80 μm³). **Reduced β globin synthesis** also results in the precipitation of unpaired α chains within red cells, causing membrane damage. This subsequently leads to the death of red cell precursors in the bone marrow (ineffective erythropoiesis) and lysis of circulating erythrocytes (extravascular hemolysis).

Patients with **β thalassemia** have decreased β globin chain synthesis, which causes **hypochromic, microcytic anemia** (mean corpuscular volume <80 μm³). **Reduced β globin synthesis** also results in the precipitation of unpaired α chains within red cells, causing membrane damage. This subsequently leads to the death of red cell precursors in the bone marrow (ineffective erythropoiesis) and lysis of circulating erythrocytes (extravascular hemolysis).

Normal erythrocytes have an area of central pallor that typically measures 1/3 of the cell diameter. Patients with β thalassemia classically have blood smears showing small red cells with an increased area of central pallor, as seen in the image above. Other common findings include anisopoikilocytosis (variation in size and shape), target cells (green arrows [see hyperlink]), teardrop cells (blue arrows), nucleated red cell precursors (orange arrows), and basophilic stippling.

(Choices A and E) Hyperchromia is characterized by reduced central pallor due to increased hemoglobin concentration and is usually associated with spherocytosis. Spherocytosis is caused by a variety of molecular defects in the genes that encode certain red cell membrane proteins (eg, spectrin, ankyrin, band 3, protein 4.2).

(Choice B) Iron deficiency often leads to hypochromic, microcytic anemia but is most commonly caused by chronic, asymptomatic bleeding (eg, slow gastrointestinal bleed, abnormal menstruation).

(Choice D) Red blood cell sickling occurs in sickle cell anemia, which is caused by an A to T mutation in the β globin gene that results in glutamate being substituted with valine at position 6.

Educational objective:
β thalassemia results in hypochromic, microcytic anemia due to decreased β globin chain synthesis. Unpaired α chains precipitate within red cells and cause membrane damage, leading to ineffective erythropoiesis and extravascular hemolysis.

References

- Alpha and beta thalassemia.
- Evaluation of microcytosis.

Genetics Hematology & Oncology Thalassemia

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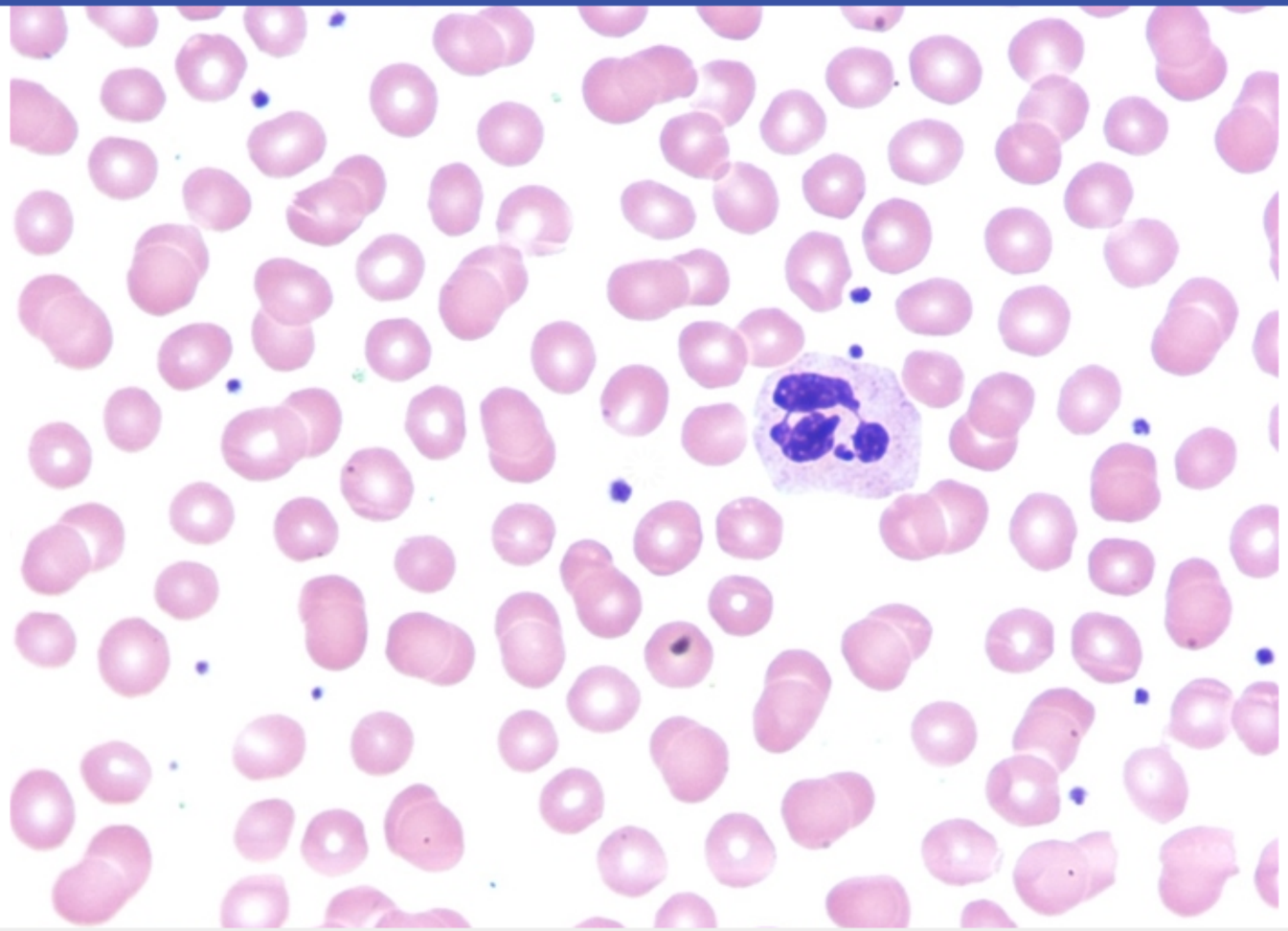

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Genetics | Hematology & Oncology | Thalassemia

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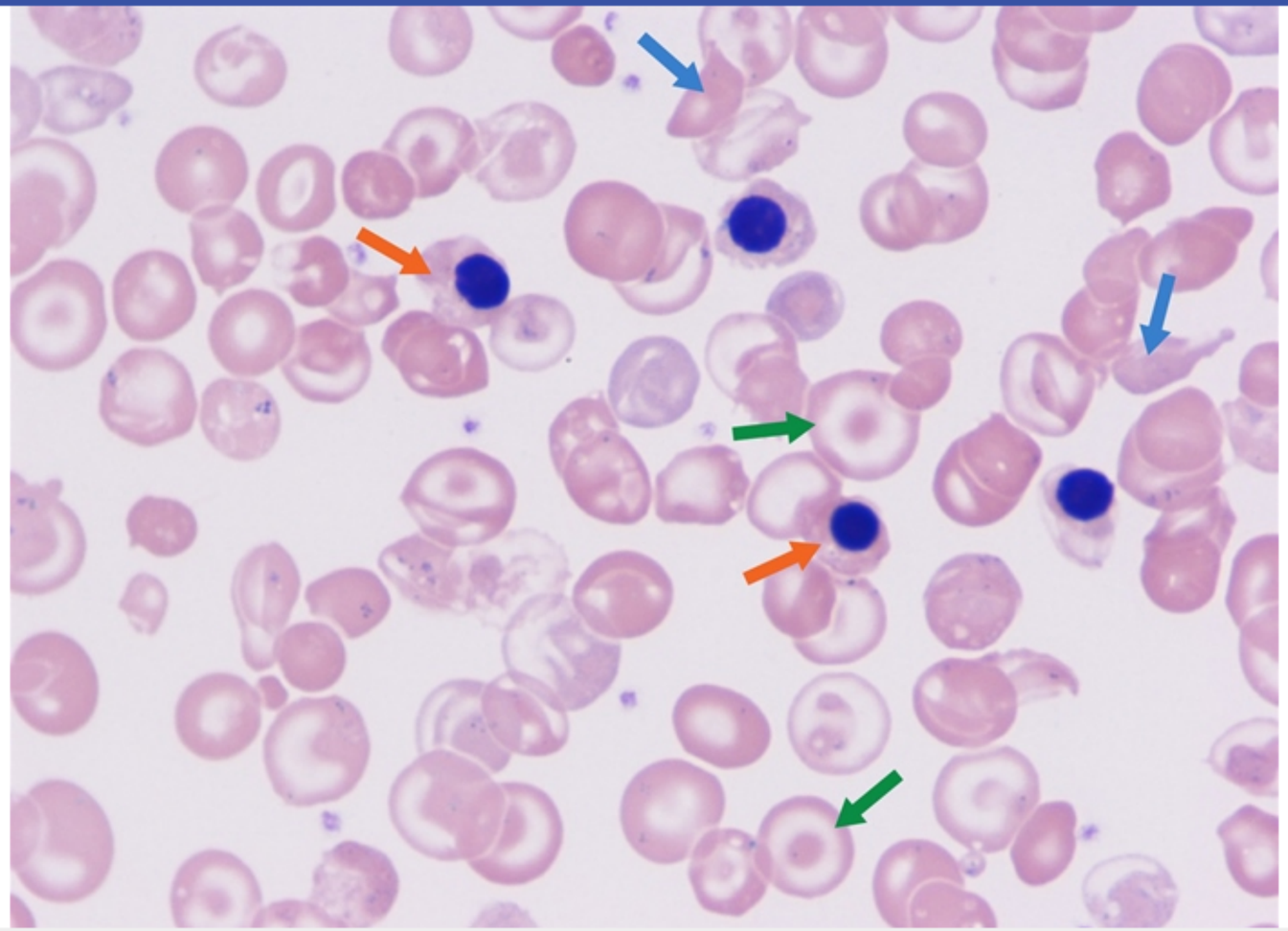

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Genetics | Hematology & Oncology | Thalassemia

A 22-year-old woman presents to clinic for a medical check-up. She has been diagnosed with Turner's syndrome. Cardiovascular examination reveals no abnormalities of the heart or aorta. She asks about her chances of having a baby. Which of the following methods could be used to achieve pregnancy in this patient?

- A. Bromocriptine therapy
- B. Clomiphene citrate
- C. Pulsatile GnRH infusion
- D. hCG therapy
- E. In vitro fertilization (IVF)

Submit

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- A. Bromocriptine therapy (0%)
- B. Clomiphene citrate (5%)
- C. Pulsatile GnRH infusion (12%)
- D. hCG therapy (1%)
- ✓ E. In vitro fertilization (IVF) (79%)

Omitted
Correct answer
E

79%
Answered correctly

02 secs
Time Spent

03/05/2020
Last Updated

Explanation

Most women with Turner syndrome (45,XO) are infertile secondary to ovarian failure. With sufficient estrogen and progestin supplementation, however, these women can develop a thick endometrial lining that is substantial enough to support a pregnancy. In vitro fertilization of Turner syndrome patients with an ovum provided by a related or anonymous donor results in pregnancy rates approaching 60%. A thorough renal, cardiac and thyroid examination should be carried out before pregnancy is attempted to reduce the potential for complications during pregnancy. Pregnancy can occur spontaneously in some patients with Turner syndrome, but the risk of spontaneous abortion, Down syndrome and Turner syndrome are all increased in such cases.

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(Choice A) Bromocriptine is a dopamine receptor agonist that inhibits pituitary prolactin secretion. It can restore fertility in women with hyperprolactinemia.

(Choice B) Clomiphene citrate is an antiestrogen that stimulates ovulation by blocking the feedback inhibition of estrogen on the hypothalamus thereby enhancing the release of pituitary gonadotropins. It is best used to achieve fertility in women with ovulatory failure who are normogonadotropic, normoprolactinemic and euthyroid.

(Choice C) Pulsatile GnRH infusion can stimulate ovulation in women who have disordered hypothalamic GnRH secretion resulting in hypogonadotropic, hypogonadal anovulation. Pituitary and ovarian function must be intact for this method to work.

(Choice D) hCG therapy can be used to trigger the ovulatory cascade in an oocyte donor when her follicles are deemed mature.

Educational objective:
In vitro fertilization using a donated ovum is the most promising means of achieving pregnancy in a woman with Turner syndrome. Pregnancy can occasionally occur spontaneously in some patients with Turner syndrome, but the risk of spontaneous abortion, Down syndrome and Turner syndrome are all increased in such cases.

Genetics | Female Reproductive System & Breast | Turner syndrome

however, these women can develop a thick endometrial lining that is substantial enough to support a pregnancy. In vitro fertilization of Turner syndrome patients with an ovum provided by a related or anonymous donor results in pregnancy rates approaching 60%. A thorough renal, cardiac and thyroid examination should be carried out before pregnancy is attempted to reduce the potential for complications during pregnancy. Pregnancy can occur spontaneously in some patients with Turner syndrome, but the risk of spontaneous abortion, Down syndrome and Turner syndrome are all increased in such cases.

(Choice A) Bromocriptine is a dopamine receptor agonist that inhibits pituitary prolactin secretion. It can restore fertility in women with hyperprolactinemia.

(Choice B) Clomiphene citrate is an antiestrogen that stimulates ovulation by blocking the feedback inhibition of estrogen on the hypothalamus thereby enhancing the release of pituitary gonadotropins. It is best used to achieve fertility in women with ovulatory failure who are normogonadotropic, normoprolactinemic and euthyroid.

(Choice C) Pulsatile GnRH infusion can stimulate ovulation in women who have disordered hypothalamic GnRH secretion resulting in hypogonadotropic, hypogonadal anovulation. Pituitary and ovarian function must be intact for this method to work.

(Choice D) hCG therapy can be used to trigger the ovulatory cascade in an oocyte donor when her follicles are deemed mature.

Educational objective:
In vitro fertilization using a donated ovum is the most promising means of achieving pregnancy in a woman with Turner syndrome. Pregnancy can occasionally occur spontaneously in some patients with Turner syndrome, but the risk of spontaneous abortion, Down syndrome and Turner syndrome are all increased in such cases.

Genetics	Female Reproductive System & Breast	Turner syndrome
Subject	System	Topic

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An autopsy was performed on a 17-year-old girl after a fatal motor vehicle collision. Her ovaries appear small and underdeveloped on gross examination. Light microscopic examination shows ovaries primarily composed of connective tissue with no follicles. Which of the additional abnormalities is most likely to be found on postmortem examination?

- A. Bicuspid aortic valve
- B. Inspissated pancreatic ducts
- C. Lens displacement
- D. Mitral valve prolapse
- E. Vaginal adenosis

Submit

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- ✓ A. Bicuspid aortic valve (85%)
- B. Inspissated pancreatic ducts (1%)
- C. Lens displacement (2%)
- D. Mitral valve prolapse (5%)
- E. Vaginal adenosis (5%)

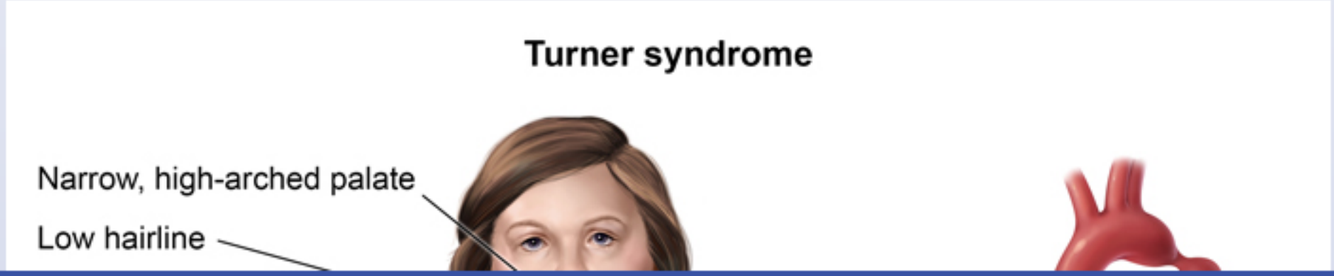
Omitted
Correct answer
A

85%
Answered correctly

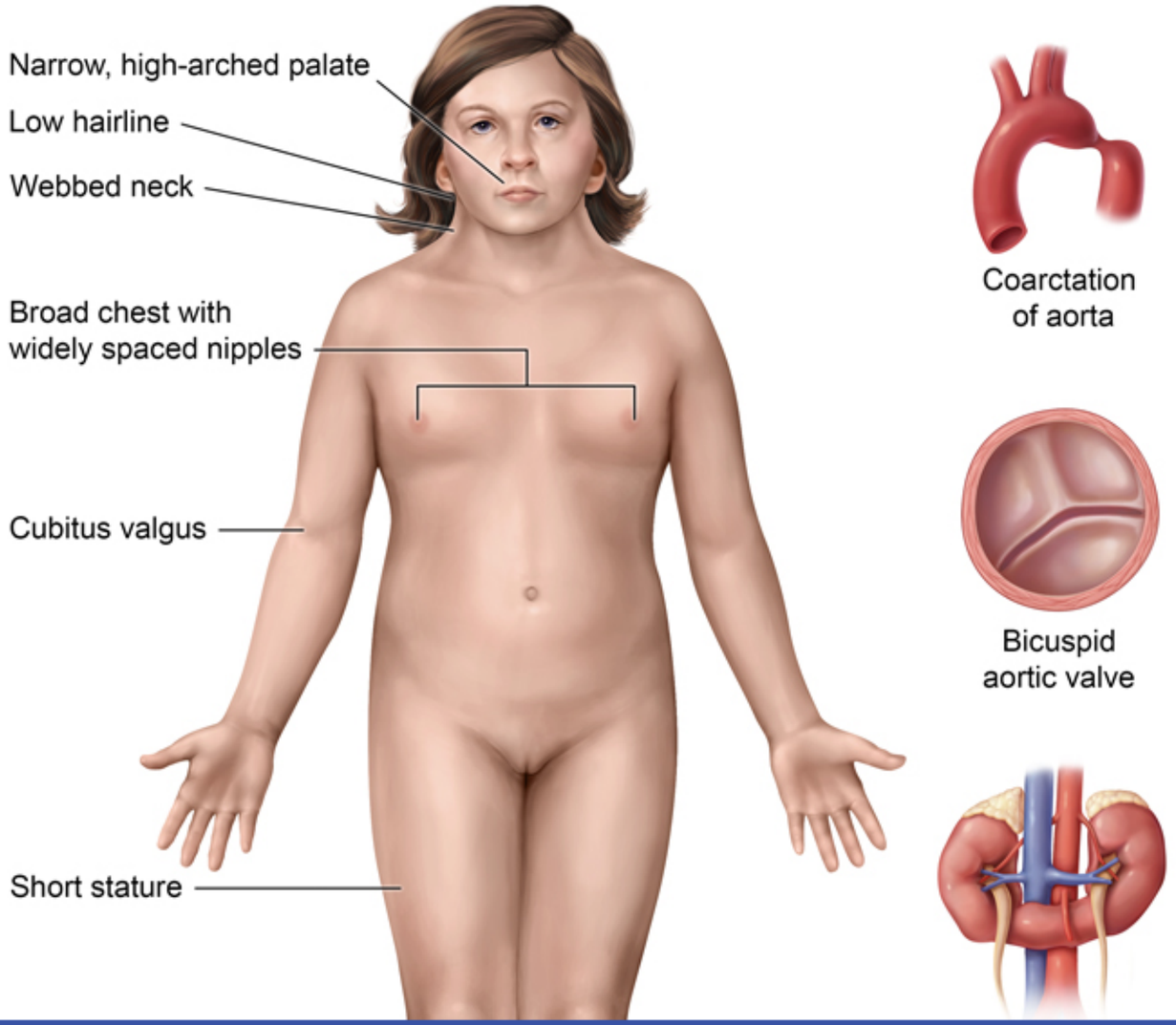
01 sec
Time Spent

02/29/2020
Last Updated

Explanation



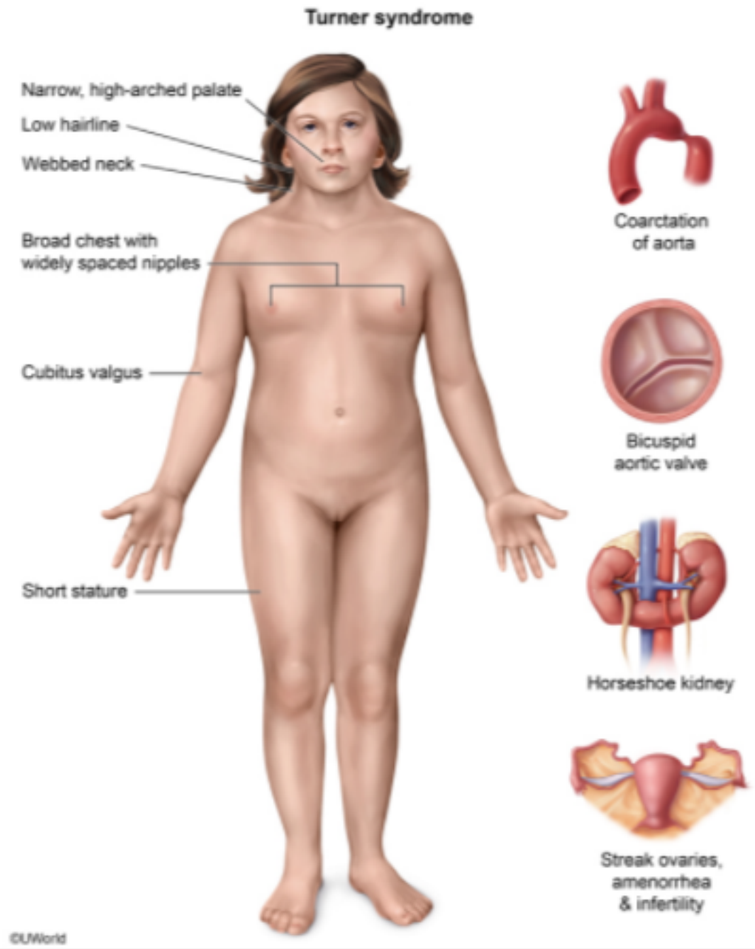
Turner syndrome



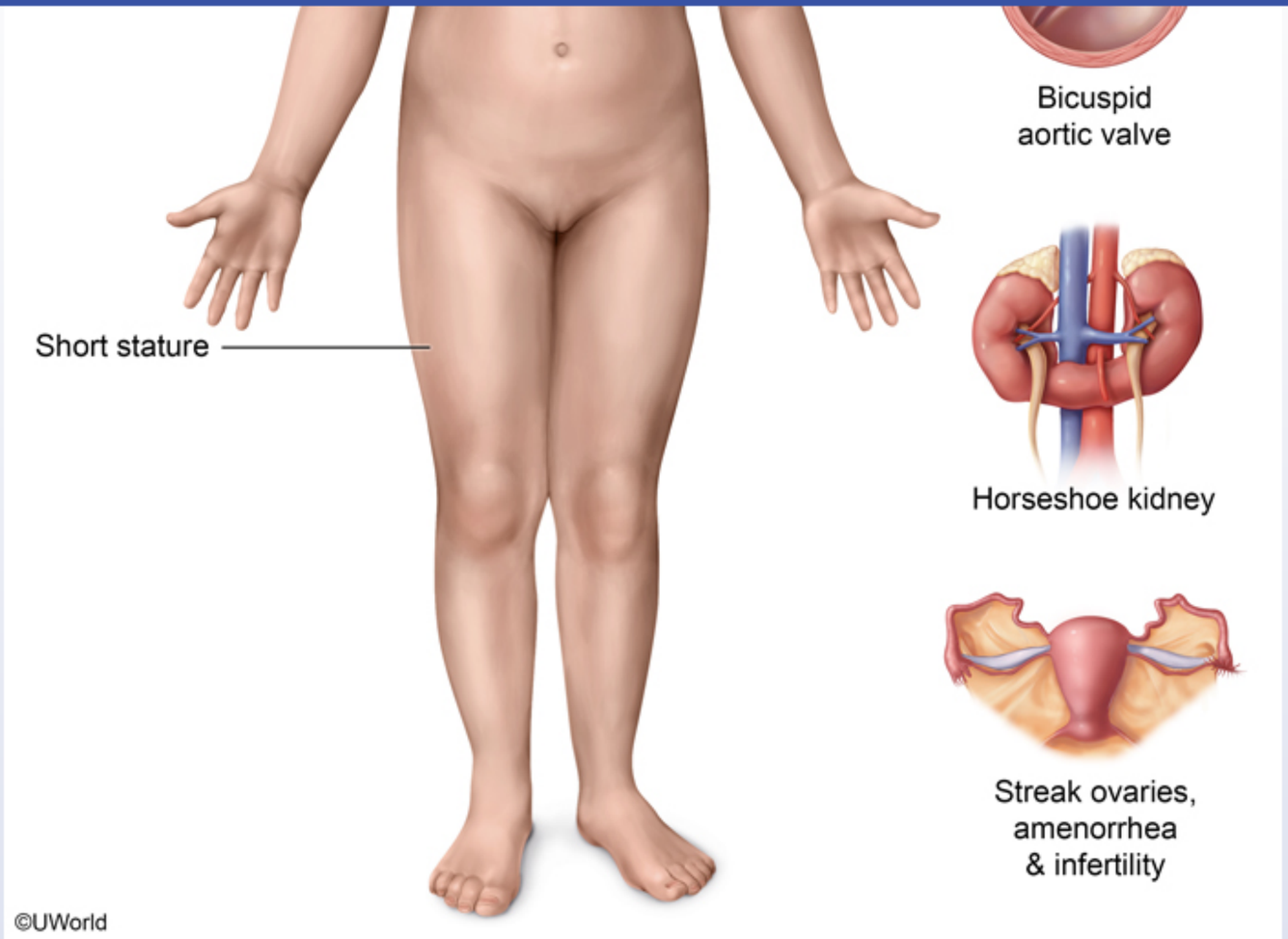
Coarctation of aorta

Bicuspid aortic valve

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card



The ovaries described in the vignette are the streak ovaries of Turner syndrome (TS). Patients with TS have normal ovarian development during fetal life. However, lack of the paternal X chromosome causes loss of ovarian follicles by age 2, as well as a karyotype of 45, X. At puberty, patients with TS usually have normal pubic hair but no breasts or menses due to ovarian failure. **Premature ovarian failure** is characterized by **high LH and FSH levels**, and TS is one of the most common causes.

The ovaries described in the vignette are the streak ovaries of Turner syndrome (TS). Patients with TS have normal ovarian development during fetal life. However, lack of the paternal X chromosome causes loss of ovarian follicles by age 2, as well as a karyotype of 45, X. At puberty, patients with TS usually have normal pubic hair but no breasts or menses due to ovarian failure. **Premature ovarian failure** is characterized by **high LH and FSH levels**, and TS is one of the most common causes.

Patients with TS also have several extragonadal abnormalities. Short stature, shield chest (broad, with widely spaced nipples), and webbed neck (broad neck with low hairline) comprise the appearance of these patients. Lymphedema may be seen at any age, including neonates. **Bicuspid aortic valve** (20%-30%) is the most common cardiovascular anomaly; other common defects include **coarctation of the aorta** (3%-10%) and aortic root dilation with an increased risk of aortic dissection in adulthood.

(Choice B) Pancreatic insufficiency occurs in patients with cystic fibrosis due to obstructed, inspissated pancreatic ducts.

(Choices C and D) Mitral valve prolapse and lens displacement are seen in patients with Marfan syndrome. These patients are also at risk for aortic root dilation and aortic dissection.

(Choice E) Vaginal adenosis is replacement of the vaginal squamous epithelium with glandular columnar epithelium. It occurs in the female children of women exposed to diethylstilbestrol (DES) during pregnancy. Vaginal adenosis is a precursor of clear cell adenocarcinoma of the vagina.

Educational objective:
Streak ovaries, amenorrhea, and infertility are the gynecologic complications of Turner syndrome (TS). In addition, patients with TS usually have short stature, webbed neck, shield chest, and low posterior hairline. Bicuspid aortic valve is the most common cardiac comorbidity.

References

- Turner syndrome: diagnosis and management.
- Aortic valve disease in Turner syndrome.

Genetics	Female Reproductive System & Breast	Turner syndrome
Subject	System	Topic

A newborn girl is evaluated in the nursery after an uncomplicated spontaneous vaginal delivery to a 29-year-old primigravida. The mother declined prenatal testing and ultrasound examination during the pregnancy. Her pregnancy was otherwise uneventful, and she took prenatal vitamins throughout. Examination of the neonate shows a posterior neck mass and bilateral nonpitting edema of the hands and feet. Femoral pulses are diminished. Neck ultrasound reveals a mass composed of cystic spaces separated by connective tissue. Which of the following is the most likely underlying mechanism responsible for this patient's condition?

- A. 21-hydroxylase deficiency
- B. Androgen receptor mutation
- C. Loss of paternal chromosome X
- D. Meiotic nondisjunction of fetal chromosome 18
- E. Partial deletion of the short arm of chromosome 5
- F. Robertsonian translocation involving fetal chromosome 21

Submit

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- A. 21-hydroxylase deficiency (3%)
- B. Androgen receptor mutation (1%)
- ✓ C. Loss of paternal chromosome X (62%)
- D. Meiotic nondisjunction of fetal chromosome 18 (11%)
- E. Partial deletion of the short arm of chromosome 5 (12%)
- F. Robertsonian translocation involving fetal chromosome 21 (9%)

Omitted
Correct answer
C

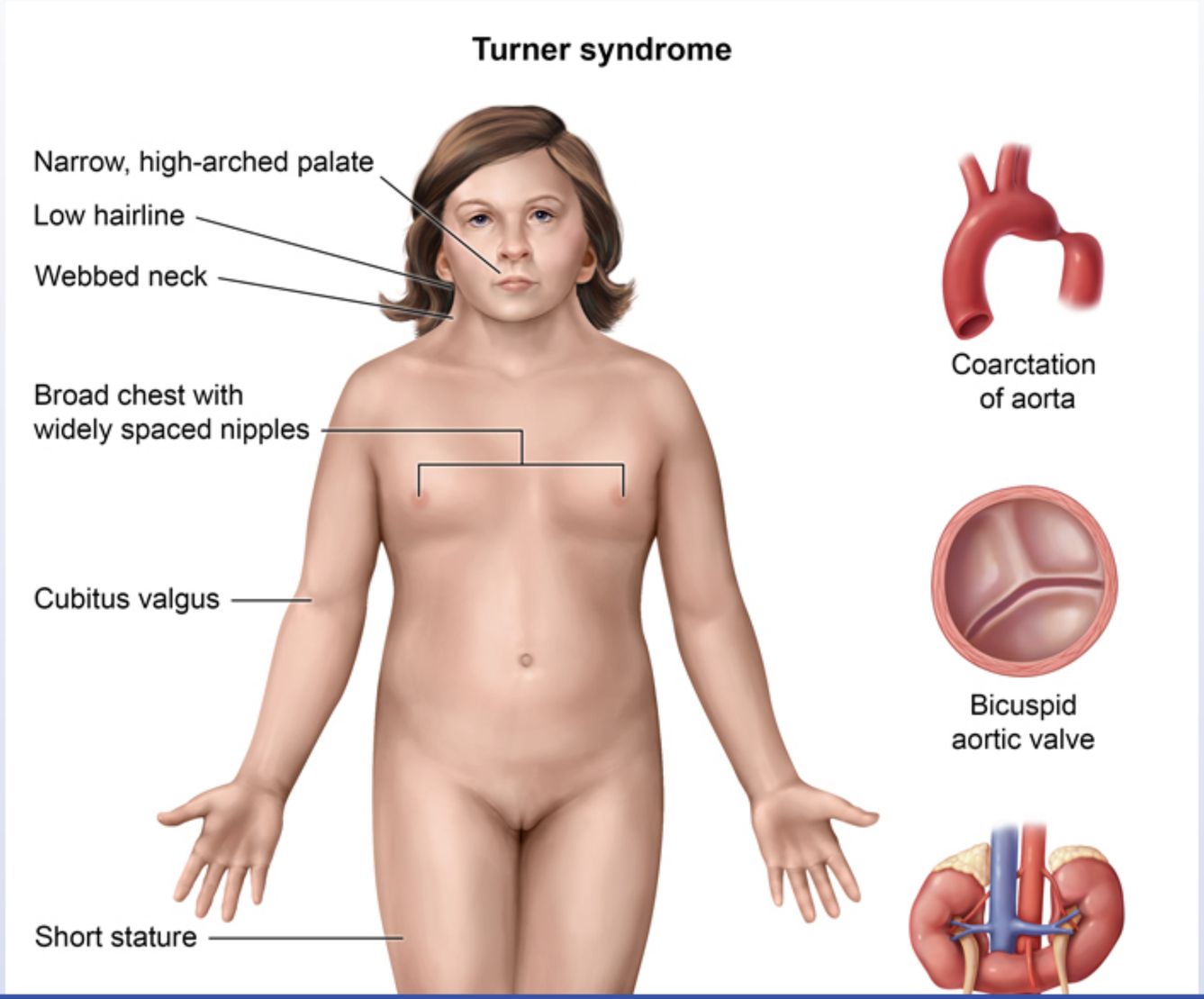
62%
Answered correctly

02 secs
Time Spent

04/12/2020
Last Updated

Explanation

Turner syndrome


Turner syndrome
Narrow, high-arched palate
Low hairline
Webbed neck
Broad chest with widely spaced nipples
Cubitus valgus
Short stature
Coarctation of aorta
Bicuspid aortic valve

This patient's posterior neck mass is most likely a **cystic hygroma**, and the bilateral extremity swelling is consistent with **lymphedema**. These findings in the context of **diminished femoral pulses** (suggestive of **coarctation of the aorta**) in a newborn girl are classic for Turner syndrome. Turner syndrome is characterized by a 45,X karyotype due to **loss of paternal chromosome X**. Both cystic hygromas and lymphedema occur due to abnormalities of lymphatic outflow in Turner syndrome. The swelling decreases with age.

(Choice A) In congenital adrenal hyperplasia (adrenogenital syndrome), patients have abnormal sexual differentiation due to defective hormone synthesis in the adrenal glands. The most common enzymatic defect is 21-hydroxylase deficiency. At birth, patients have ambiguous genitalia (girls only) and salt wasting (hypotension, hyponatremia).

(Choice B) Androgen insensitivity syndrome results from a defect in testosterone receptors. The typical presentation is a 46,XY adolescent who appears phenotypically female but has primary amenorrhea due to the absence of an internal female reproductive tract and the presence of cryptorchid testes.

(Choice D) Trisomy 18 (Edward syndrome) is usually caused by meiotic nondisjunction. These patients have multiple anomalies, including cardiac defects, clenched fists, rocker bottom feet, omphalocele, and low-set ears.

(Choice E) *Cri du chat* is most commonly due to a de novo partial deletion of the short arm of chromosome 5 (5p-). Patients with *cri du chat* syndrome typically have a round face, catlike cry, and microcephaly.

(Choice F) Down syndrome (DS) results from meiotic nondisjunction or Robertsonian translocation involving fetal chromosome 21. These patients have a flat face, oblique palpebral fissures, and epicanthal folds. Atrioventricular defects are the most common cardiac anomaly. Although cystic hygromas can occur in patients with DS, the absence of the dysmorphic features of DS makes this diagnosis unlikely.

Educational objective:
Turner syndrome (45,X) manifests in the neonate with lymphedema and cystic hygromas. Short stature, primary amenorrhea, and aortic anomalies are the other important clinical features.

References

- Turner syndrome: diagnosis and management.
- Aortic valve disease in Turner syndrome.